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PSYCHIATRIC COMPARISON OF ARTIFICIAL MENOPAUSE AND THE EFFECTS OF HYSTERECTOMY

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MENTAL disturbances occurring in women at the menopause are commonly assumed to be due to the menopause, but the explanation of this differs according as they are mild or severe. If mild—taking the form of anxiety and depression, along with neurovascular symptoms such as flushing—endocrine changes are held responsible, and the benefits of replacement therapy with female sex hormones in most cases confirms the explanation. If severe, however—usually a psychosis with gross anxiety and depression—constitutional predisposition and psychological factors are more often invoked than endocrine ones : the illness is similar in form to those occurring in the involutional phase of life, when the menopause has perhaps for years been a closed chapter, and from this and the frequent failure of œstrogen-therapy to relieve the condition it has been inferred that the endocrine changes are of little consequence, many writers pointing rather to the causes for unhappiness and frustration which may lie in the obvious cessation of reproductive life. It is hard to credit that a mild mental disturbance at the menopause could be due to different causes from those of a severe one of the same type at the same time of life. It seemed that one way of studying the problem would be to compare the incidence of mental disturbance in women who had suffered an artificial menopause through surgical removal of the ovaries with the incidence in women whose uterus had been removed before they had reached the menopause. In both groups of women the periods would have ceased and reproductive life would be clearly at an end : the psychological factor would therefore presumably be equally operative in both

and any inherited constitutional factors would be as likely in one group as in the other. In those on whom oophorectomy had been performed, the endocrine factor would also be present : if they had a higher incidence of mental disturbance than those with hysterectomy, it would be the endocrine change that was likely to be responsible.

The clinical difficulties in deciding whether a mental disturbance is menopausal are considerable. Menopausal illnesses are in form indistinguishable from neuroses or insanity of the same age period in men, or in women who are still years away from their menopause. The menopause, moreover, is a hard thing to time exactly. The cessation of the periods may be deceptive. Some psychoses (Farrar and Franks, 1931) called menopausal turn out to have been only psychoses which were accompanied by a temporary amenorrhœa. Direct studies of menopausal psychoses have been somewhat unsatisfactory, and the significance of the menopause in causing the depressions and anxieties of middle-aged women doubtful, even when the two undoubtedly coincide. The following investigation was intended to throw light on the rôle the menopause may play in provoking mental changes, whether as a direct sequel of the endocrine changes, or as a psychological reaction to permanent and certain loss of fertility, the " change of life."

Sixty-seven women who had been operated on by the gynæcologist were the subject of study. Forty-two of these had had their uterus removed, one or both ovaries being left intact. The twenty-five others had had their uterus and both ovaries removed. The names and notes of the patients were generously put at our disposal by Mr. W. Gilliatt, C.V.O., and Mr. A. C. Palmer, O.B.E., who had operated on them at King's College Hospital, and to whose co-operation we owe the opportunity of carrying out the inquiry. The patients were visited in their homes on one or more occasions, four years (in some cases five) after the operation, and details about their state before and, especially, since the operation obtained from them ; in some instances also from their nearest relatives. Of 128 patients operated on between the years 1930 and 1932, 66 were traced and visited, eleven had died (one of these is included in the present inquiry), 31 had left London and could not therefore be visited, and 20 could not be traced at all. None had been certified or admitted to a mental hospital : information supplied by the Board of Control confirmed this.

As the endocrine changes entailed by double oophorectomy are believed (Kurzrok and Smith, 1938) to be closely akin to those of the normal menopause, though more sudden, any conclusions drawn from psychiatric differences between the women whose ovaries had been removed (who may be called the castrated women) and those who still had one or both ovaries but no uterus, are presumably applicable to the normal menopause. Certainly for the majority, or all, of the castrated women in this series there was nothing in the psychological situation to make it different for them from that confronting the others (who had had a hysterectomy)—or from that of a woman passing through the normal menopause, except in its abruptness. This would not be true unless each of the three groups mentioned were of similar composition as regards other factors bearing on the mental state :

a preponderance in one group, for instance, of patients with a history of previous mental illness would partly invalidate any conclusion of the kind mentioned. The composition of the two groups of women investigated here showed no gross divergency in such respects.

Nature of the Material

The patients whose ovaries had been removed (Group A) were an older group, on the whole, than the others, as may be seen in Table 1. This is inevitable, since the surgeon will not often remove both ovaries in a woman unless she is near the menopause (or past it : no such cases were included in this study), and on the other hand it was desirable for the purposes of the investigation that the " sterilized " group should not be of an age at which spontaneous menopause was likely to occur within the period of observation. Incomplete attainment of the latter aim was a handicap in assessing the findings, as will be seen later.

TABLE 1.—NUMBER OF PATIENTS IN AGE-GROUPS

	18–35 YRS.	36–40 YRS.	41–45 YRS.	46–50 YRS.	51–55 YRS.	TOTAL
Group A	—	2	6	13	4	25
Group B	11	12	9	10	—	42

The two groups did not differ in respect of intelligence and past working capacity. In physical health, prior to the illness for which they had been operated on, the two groups did not notably diverge : it was remarkable that either bilious attacks or anæmia, or both, were reported frequently (in 7 of the 25 patients in Group A, and in 14 of the 42 in Group B).

Five of Group A had had a neurotic illness at some time in their lives before the illness leading to their operation : so had nine of Group B. Eleven of Group A and 20 of Group B had all their lives up to the operation been of tense, worrying, restless temperament : it is obvious that only the most general statement on this matter can be accepted in view of the interval of years, the lack in most cases of detailed corroborative evidence, and the dependence of such traits upon varying circumstances. Unintentional falsification of their past psychological traits is especially likely to occur in neurotic persons.

The average age of onset for menstruation had been 14 in both groups and there was no noteworthy difference in the incidence of menstrual pains, depression, irritability, etc., in the two groups. All but two of Group A were married, and all but five of Group B : the average age at marriage of Group A was 24, of Group B 23. Of the married women five in Group A were frigid, and nine in Group B : in nine cases, no information was obtained, or it was too vague

to be used. The married women in Group A had fewer children than those in Group B. (See Table 2.) There had also been fewer miscarriages among the women of Group A.

TABLE 2.—SHOWING HOW MANY WOMEN HAD A GIVEN NUMBER OF CHILDREN

	NUMBER OF CHILDREN											TOTAL CHILDREN
	0	1	2	3	4	5	6	7	8	9	10	
Group A	4	7	6	1	1	1	1	1	—	—	—	44
Group B . .	6	8	7	4	6	—	3	1	1	—	1	101

The diseases for which gynæcological operation was performed on Group A were uterine fibroids in 15, ovarian endometrioma in two, ovarian cyst in five, inflammation of uterus or tubes in four ; in some cases more than one of these was present. Polyps and adenomyomata were also found. The reported duration of symptoms varied between 1 month and 16 years ; it was more than 1 year in eight cases. In Group B the diversity of diseases was greater, and they included fibroids, adenocarcinoma, endometrioma, polyps, cervicitis and endometritis, chronic subinvolution, prolapse, retroversion, and salpingitis ; 16 had fibroids. There were also four in whom pregnancy was complicated by heart disease, etc., or by pelvic deformation that had already called for one or more cæsarean sections. The duration of symptoms had been much greater than in Group A : 28 of the women had had symptoms for more than a year, and 13 of these had complained of symptoms for 4 years or more before the operation. All but two (who had only double oophorectomy) of Group A had panhysterectomy and bilateral salpingo-oophorectomy : in Group B, hysterectomy in one or other form, sometimes with and sometimes without the removal of the Fallopian tubes, had been carried out. There was no striking difference between the two groups in respect of post-operative complications or duration of convalescence : where the latter was prolonged, and the patient did not return to her ordinary work within a year after the operation, this seemed referable in both groups to the occurrence of menopausal symptoms or sequelæ, as described in the next section, rather than to the actual operation. Such a distinction is, of course, not easy to draw, but may be illustrated by the frequent report by the women that their hair had fallen out just after the operation and they had lost weight, but that both these losses had been fully made good after a few months ; changes of this sort would probably be directly attributable to the loss of blood, trauma, etc., of the operation : where, however, superfluous hair had developed, or the patient had become much fatter, the changes seemed more likely to be due to the artificial menopause.

Effects

To separate the physical from the psychological features of the menopause offers practical, as well as biological and theoretical difficulties. Flushings, for example, may be evoked by situations in a psychogenic way, e.g. in the familiar mild anxiety attack, as well as occur physiogenically, e.g. in response to heat or exertion. So many of the recognized menopausal symptoms are in the domain of the vegetative nervous system, where physical and psychological are hardly distinguishable, that this difficulty is to be expected.

For convenience the symptoms inquired after have been divided into two sets. In the former of these, of a more physical nature, are flushings, giddiness, breathlessness, headache, increase in weight, growth of hair, pains, cramps or other discomforts in the limbs, disturbed sleep, changed appetite, libido, and occurrence of any cyclical phenomena such as periodic swelling of the breasts. In the latter, or psychological, set are irritability, depression and lassitude, anxiety, impairment of memory or ability to concentrate, and restriction of interests. Any other neurotic symptoms, and the patient's attitude towards the operation, were also enquired into. The relationship of the anomalies found to each other, to the patient's previous history and personality, and to her present circumstances was investigated as it would be in any psychiatric case.

(*a*) *Physiological.*—Flushings had occurred in all the castrated patients but one (a woman of 48 who had been likewise free from most of the other menopausal discomforts). There was considerable variation in the time of onset, total duration, and severity of the flushings. In three women, aged 45, 46, and 48, they had been noticed for a year before the operation, though other indications of the menopause had not been evident in two of them : in another woman whose periods had ceased at 33, i.e. 7 years before the operation, without discoverable physical cause, the flushings did not come on until 2 years after the operation. Four of the women had no flushings until 1, 2, or 3 years after the operation : another first had them 6 months after the operation. The total duration varied between 6 months and 5 years : when lengthy they had gradually lessened in severity and frequency after about two years, except in one patient, aged 41, in whom they had become worse as time went on. In three women they had at one time been very severe, in 11 they had been pronounced, in 10 definite but slight ; it was found impracticable to grade them, as Albright (1936) did, according to frequency per day, because they had gradually changed in frequency, and reliable data were therefore not forthcoming. Giddiness, breathlessness, and headaches seemed so often to be concomitants of the flushing attacks that it is appropriate to consider them at this point. Eleven of the patients had giddiness, along with flushings ; it was never severe and never led to falls or syncope. Breathlessness was reported by 10 of the same 11, with the flushing ; and by two others, also with flushing : it was not severe, and was occasionally the accompaniment of palpitations. Headaches were reported as having developed after the operation, in 10 women, of whom only one had them severely.

The same phenomena in Group B were by no means as infrequent as had been expected. Thirty-two women had flushings, 12 fairly severely. In two they had been noticed before the operation. In 12 they had begun within the first 6 months after the operation and had continued for periods varying between 3 months and 4 years. In 14 they had begun from 1 to 5 years after the operation ; the average age of these women at the time of operation was 40, the youngest being 30 years old. Giddiness was reported in 22, always with flushing, except in one woman with heart failure ; in another, both giddiness and flushings had since the operation coincided with the cataleptic attacks to which she had been prone from the age of 21. Breathlessness was a symptom in 23, but many of these had complained of it for months or years before the operation. It was more often said to be brought on by exertion in this group than in Group A. The concurrence of flushing with giddiness and breathlessness in the same patients was as striking in Group B as in Group A.

Weight.—Sixteen of Group A had increased in weight, some grossly. Eighteen of Group B had increased, though in two of these the weight had later returned to normal ; the increase was often between 2 and 3 stone ; in one woman (aged 39) 4 stone.

Hair.—Four of Group A had had superfluous hair growing on chin and upper lip since the operation (in one of them to a disfiguring extent). This had not occurred in any of Group B : one of them, however, had been temporarily quite bald after the operation.

Sleep.—Six of Group A and four of Group B slept badly. Two of Group A and seven of Group B had poor appetite or indigestion.

Pains.—Fifteen of Group A complained of pains (chiefly backache) : possibly rheumatoid joint changes were reported in four. Thirty-three of Group B had pains (chiefly discomfort in loins ; also in abdomen, limbs, or genitals). In both groups there were many who reported dryness and discomfort in their genitals, sometimes making coitus impossible. Five of Group A and 14 of Group B had cramps in their legs or numbness and tingling.

Cyclical changes were sought for, especially in regard to sensations in the breasts. Of Group A seven, and of Group B 26, reported more or less periodic feelings of the kind formerly associated with menstruation. In only five, however, all in Group B, were these noticed to occur with monthly regularity.

Libido.—Enquiry into the effects of the operation upon sexual desire and gratification was hampered not by their reticence, for they were almost all willing to supply the desired information, but by the preceding frigidity which in so many of them had for years made overt sexuality empty or disagreeable to them. Apart from the two single women, data were obtained from all the patients in Group A : 13 had now less libido than before the operation, and little or no gratification, pain in coitus being apparently responsible for this in four of them. None (including those who had been frigid before) reported any increase of desire since the operation. In Group B no satisfactory information on the point was obtained concerning six patients : of the remainder 16 had lessened libido and two reported an increase, but it seemed in these two that

removal of the fear of pregnancy, which had previously interfered with sexual gratification, was responsible for the apparent change.

(*b*) *Psychological.*—There was only one instance of insanity after the operation : this was a very brief episode occurring in a previously normal woman of 38, while she was still in the surgical ward recovering from a cæsarean section and sub-total hysterectomy.

Some of the features conspicuous in involutional melancholia were not discoverable, even in attenuated form, in any of these patients : this is true of paranoid tendencies and of hypochondriacal notions about the bowels.

Anxiety, tension, and restlessness or phobias were present in 14 of Group A and 35 of Group B. Eight of these in Group A and 16 in Group B had always been of a worrying temperament or had had fears before their operation. In only five of Group A and seven of Group B was the anxiety severe enough to be regarded as troublesome ; none of the patients had sought treatment for it. In many instances of Group B and two of those in Group A there were adequate external grounds for worrying. A majority of the patients who in each group reported severe flushings said also that they got easily flustered. Five patients mentioned spontaneously their fears about cancer, due to ignorance of the nature and purpose of their operation : the impression was gained that many more, if questioned directly on the point, would have reported this too.

Depression, with tiredness, lack of confidence, and difficulty in concentration, was reported in 15 of Group A and in 26 of Group B. In all of those in Group A it had come on soon after the operation and had gradually become less. In Group B it had less obvious relation to the operation, in many instances being more a continuation of ill-health and general weariness that had gone on for a long time before the operation. In both groups it was variable or intermittent. In three of Group A and six of Group B it had been fairly severe, accompanied by suicidal inclinations, much weeping, hopelessness, or self-reproach : in one patient of Group A it had centred in the disfigurement due to hair growing on her chin and lip, and in several of Group B in their notions about cancer. In none of the cases had there been hospital treatment for the depression. Variability of mood was frequently reported in both groups.

Irritability occurred in nine of Group A and 14 of Group B ; all these had also anxiety. Memory was said to be impaired in 10 of Group A and in 13 of Group B. Obsessional or hypochondriacal symptoms had occurred in five of Group A and in five of Group B.

Altogether there were 13 in Group A, and 17 in Group B who had definite and troublesome neurotic symptoms of one kind or another.

Discussion

The differences between the two groups, in respect of psychological disturbances after the operation, would not appear to be significant ($X^2=0{\cdot}44$) especially in view of the nature of the data in question and the difficulties of recording and assessing them on any uniform scale. From this it might

perhaps be inferred that the endocrine factor in menopausal anxiety and depression is negligible, and that the latter must be regarded as a psychological reaction to the loss of fertility, with all its implications. There are objections to both these inferences. The investigation was not designed to provide any positive information about the latter of them ; one could go no farther than to say, if endocrine influence be excluded, that in both groups there was the same situation, due to their surgically produced inability to have more children, and that it might have acted psychologically to produce much the same results in each. Alternative interpretations would have to be considered, based on the previous personality and disposition to neurotic instability in these patients, or on the effects of a long, alarming, or exhausting illness, and on the physical and psychological stresses of a severe abdominal operation : the two latter issues point to the difficulty of comparing these patients, at any rate during the first year of their post-operative period, with women passing through the menopause spontaneously. The psychological disturbances reported by Binder (1937) in women after sterilization by tubal resection and by Krauss (1932) in castrated women show how many factors need consideration. But, apart from this, the inference as to endocrine factors being negligible cannot be drawn, since it seems likely that in some of the non-castrated patients endocrine changes similar to those of the normal or artificial menopause have ensued during the four post-operative years covered by the investigation. It is true that the patients in the non-castrated group were on the whole younger than the other, in whom presumably the imminence or suspected occurrence of the menopause was the main factor in deciding the surgeon as to whether he would leave the ovaries or not, but still 19 of them were over 40, and all but 10 were over 35. There is, further, the possibility, much more remote and controversial, that removal of the uterus has an influence on endocrine activity, especially of the ovaries ; experiments on the immediate effects in primates have not confirmed the positive findings reported in some lower mammals, but there are no experiments to show whether hysterectomy hastens the inevitable onset of the menopause. Whatever the mechanism, more than half of the women in this series whose ovaries had not been removed developed the physical concomitants of the menopause during the post-operative period investigated ; it is reasonable to suppose, therefore, that they may have been passing through a phase of endocrine changes similar to those of the castrated women.

Physical, especially vasomotor, phenomena, such as hot flushing, being more reliable and specific than psychological ones as an indication of the menopause, and most writers concurring in the view that they are due to endocrine changes, it is necessary to see how many of those in each group who showed pronounced psychological changes also had troublesome physical changes of the menopause. In the 13 affected patients of Group A there were eight with severe flushings, etc., and in the 17 of Group B eight also. If, however, all those with definite psychological disturbances who had flushings at all, with or without other physical phenomena associated with the menopause, be included, then there were 13 of these in Group A and 11 in Group B, i.e. all of those in

Group A who were showing pronounced neurotic symptoms were showing physical evidence of the menopause, as would be expected, and two-thirds of those in Group B. The remaining six patients with psychological illness in Group B suffered from depression closely related to their previous personality and to troubles (financial and domestic) that they had had to cope with during the ensuing years.

It is obvious that many of the uncertainties in this investigation could have been avoided, without detriment to comparability, if the patients had all been under the age of 35 (so that a spontaneous menopause would have been improbable in most of the non-castrated women), and if regular examination of the patients, including measurement of the output of œstrogen and gonadotropic hormone, had been carried out at 6-monthly intervals during the 4 or 5 years after the operation. Unfortunately these conditions could not be met ; the reasons are obvious. The clinical findings collected in the way described are not, however, barren. They indicate that even though predisposition to mental illness, and stresses of daily life (poverty, bereavement, illness) could be held to account, in part, for the neurotic symptoms that developed, there is a probably significant association of these symptoms with the accepted phenomena of the menopause. It is, moreover, evident that the psychological disturbances accompanying the menopause are not a clinical entity, but exhibit in more pronounced form the individual tendencies already manifest in these patients long before the operation. The same is probably true of the most severe " menopausal " psychosis.

Summary

It was thought that the differences in neurotic symptoms between women whose ovaries had been removed and those who had had only a hysterectomy might throw light on the relative causal importance of endocrine changes and psychological reactions.

The findings in 25 " castrated " women and 42 with hysterectomy are recorded for the 4 years after the operation.

Grounds are given for supposing that in many of the non-castrated women the menopause had subsequently supervened, thus accounting for the finding that there were only statistically insignificant discrepancies between the two groups in respect of neurotic symptoms.

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ANTIBODIES TO BRAIN AND THEIR RELATION TO DEMYELINIZATION

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THE occurrence of encephalomyelitis or other neurologic disorders during the Pasteur treatment of rabies has stimulated interest in recent years in the relation of parenteral injections of brain to demyelinization in the nervous system. A short review of the subject is given by Hurst as a preliminary to his own report on an attempt to produce such lesions in rabbits. Hurst (1932) and later Schwentker and Rivers (1934) were unable to demonstrate any changes in the nervous system of rabbits receiving repeated injections of brain. Rivers (1933, 1935) and his co-workers have, however, shown large areas of demyelinization in the cerebrum of eight of sixteen monkeys which had received from 46 to 85 intramuscular injections of brain emulsion and brain extract. They likened the picture to that of Schilder's disease in man, although many eosinophils and unusual giant cells not characteristic of this disease were observed about the areas of myelin destruction.

It has been shown by Brandt, Guth, and Müller (1926) and Witebsky and Steinfeld (1928) that brain antibodies are formed in rabbits by the injection of heterologous brain tissue. Schwentker and Rivers report the presence of such antibodies on injection of homologous brain combined with pig serum, vaccine virus, or brain which has undergone autolysis. The suggestion has been made that degenerative diseases may be due to the formation of autogenous antibodies against the tissue affected. Masugi (1932), Smadel (1936), and others have produced glomerulonephritis in animals by reinjecting antikidney serum. The serum was obtained by repeated injections of kidney emulsion of one animal into another. It seemed worthwhile to determine whether a heterologous antibrain serum might not, when reinjected, bring about lesions in the nervous system.

Methods

Albino rats (Glaxo strain) and rabbits were used. With a sterile technique, the rats' brains were removed immediately after killing the animal. The brain was first cleared of blood by perfusing with sterile normal saline through the aorta until the return from the vena cava was clear. The brains were then minced with scissors and ground without an abrasive in a mortar until a smooth paste was formed. The emulsion was made by mixing the paste from 20 gm. of rat brain with 80 c.c. of normal saline and 20 c.c. of pig serum. As a

* This work was done while Dr. Kolb held a John and Mary R. Markle Foundation Fellowship.

preservative phenol was added to make a 0·5 per cent. solution. The emulsion was subcultured and rejected if growth occurred in the culture medium.

Intraperitoneal injections of this material were given three times weekly for the first month and twice weekly thereafter. Five c.c. were injected the first week, 7·5 c.c. the second, and 10 c.c. thereafter. The rabbits were bled at the end of the fourth and twelfth weeks, when complement fixation tests for brain antibodies were performed.

Another series of rabbits received kidney emulsion prepared in the same way, though omitting the pig serum. This was given in similar doses.

The rats receiving blood serum intravenously from the rabbits injected with rat brain or kidney were divided into several groups. The first group were those who received serum from the rabbits after 1 month of brain injections. The second group were those who received serum from the rabbits after 3 months of injections. The latter group was divided into three subgroups : (1) those receiving serum from rabbits injected with brain emulsion and pig serum ; (2) those receiving serum from rabbits injected with kidney emulsion ; (3) those receiving normal rabbit serum. The amount of serum given intravenously at one time varied from 0·15 to 1·0 c.c. Five rats were included in each subgroup.

After death or after killing the rats the various organs and the brains were removed and fixed in 15 per cent. formol-saline. The internal organs were embedded in paraffin and stained with iron hæmatoxylin and Van Gieson. The rat brains were frozen, sectioned and stained with Sharlach R. and hæmatoxylin.

Results

Rabbits.—Six rabbits received injections of rat brain, one of cat brain, and one of kidney emulsion. Of the animals receiving rat brain emulsion plus pig serum, three started to lose weight after the third injection and two died suddenly after the sixth. In every instance it was possible to establish the cause of death. The first animal showed a long tear in the gut. The second and third died of peritonitis, the former within 24 hours of the last injections. The third became paralysed in the hind-quarters after the fourth injection, but was well again the next day. The animal then rapidly lost weight and was weak in the hind limbs immediately after the next injection and died following the sixth injection. A large abscess was found pointing in from the parietal peritoneum.

The other three rabbits gained weight and received respectively 29, 25, 24 injections of brain emulsion. The rabbit given cat brain received 24 injections and the one receiving kidney 29 injections. These also remained in good health and gained weight.

Complement fixation tests using a dilution of the original saline emulsion of rat brain or kidney as antigens were made at the end of the first and third month of injections. Serum from all the rabbits were set up against both antigens. At the end of the first month no organ specific antibodies were present in any of the sera ; that from animals receiving brain as well as from the one receiving kidney completely fixed the complement in the presence of both kidney and brain antigens in dilution of one to forty. After three months, however, the reactions were organ specific. Serum from rabbits receiving

brain emulsion plus pig serum in dilution as high as 1/80 fixed complement in the presence of brain antigen. No complement fixation took place with kidney antigen except in one instance. In rabbit 7 complement was fixed in the presence of both antigens, but dilutions of serum were possible to 1/160 in the presence of brain and only 1/40 in the presence of kidney.

The serum from the animal receiving cat brain fixed complement in the presence of both cat brain and rat brain antigen, the former to a dilution of 1/40 completely and with 30 per cent. hæmolysis at 1/80 and the latter completely to 1/160. The antibodies are thus not species specific.

Rats. Group 1.—The first group of rats which was given serum showed no unusual behaviour during observation over a 2-months period. The maximal total amount of serum containing brain antibodies given to any rat was 3·0 c.c. The maximal total amount of serum containing kidney antibody given was 4·3 c.c. The animals were then killed with ether. No abnormal changes were seen in the tissues studied after death. It may be said that the rabbit serum at this time probably did not contain adequate amounts of brain or kidney antibody or toxin.

Group 2, *subgroup* 1.—Five rats were given serum from the rabbit inoculated repeatedly over 3 months with kidney emulsion. One rat died after three intravenous injections totaling 1·4 c.c. of serum, and another after receiving 4·4 c.c. of serum in seven injections. This rat showed marked ascites for a week before death. The urine contained much cellular debris, 0·15 gm. per cent. of protein, and urea amounting to 388 mgm. per cent. The other three animals were killed with ether ; one showed great ascites, the others had no fluid in the abdominal cavity. These rats had received totals of 8·2, 5·4, and 5·7 c.c. of serum given in seven to eleven divided doses partially intravenously and partially intra-peritoneally. Before death blood urea determinations were respectively 119·0, 196·0, and 82·4 mgm. per cent. Urine and a blood pressure determination were not made as we were primarily interested in the problem of glomerulonephritis.

At autopsy the kidneys grossly were very swollen, soft, a pale greyish colour, in contrast to the ruddy, firm-textured organ of the normal rat. The capsule peeled easily from the organ. Microscopically both glomeruli and tubules showed marked cellular changes. Many tubules were greatly distended and filled with a colloid-like substance, while the walls of others showed extensive cellular proliferation, the lumen in places being obliterated. Many cells were swollen and contained colloid. Parenchymatous cell proliferation was also present. In the glomeruli there were a proliferation of cells and destruction of glomerular outline. In some areas the condition appeared to have progressed to one of cellular degeneration of the glomerular cells.

Subgroup 2.—The rabbits which had received brain emulsion and pig serum regularly for three months acted as donors of serum to this group. These six rats received respectively 6·6, 7·0, 7·3, 5·5, 5 and 5 c.c. of serum in eight to ten injections spaced at 2 to 5-day intervals. At no time was their behaviour unusual in any way. Blood ureas on two at the end of the series of injections equalled 25·2 and 45·2 mgm. per cent.

After killing the animals with ether and examining the organs and brains as before, no pathological changes could be found.

Subgroup 3.—These rats received serum from a normal rabbit. These animals showed no ill effects and after death their organs were normal on both macroscopic and microscopic study.

Discussion

The inability to produce any lesions by the technique employed here throws doubt on suggestions that the demyelinizing diseases are due to the development of antibodies against brain tissue antibrain antibodies or to the autogenous development of a " cerebrotoxin." The fact we were able to produce glomerulonephritis as Masugi, Smadel, and others have done indicates that the technique employed was not at fault. The inability to produce lesions in either kidney or brain by intravenous injection of normal rabbit serum offers a negative control for these experiments.

It is interesting that we were able to give repeated massive intraperitoneal injections of brain emulsion to four rabbits over a period of three months without ill effect. Schwentker and Rivers noticed no weight loss in their large series of animals when giving injections intraperitoneally. On the other hand, Hurst concluded that brain emulsions had a definite toxic effect and caused weight loss with eventual death. He gave his injections intramuscularly. We are disinclined to believe that brain tissue *per se* has any toxic properties.

The results of the complement fixation tests is in agreement with those of Brandt, Guth and Müller, and Witebsky and Steinfeld, who described the presence of organ specific antibodies to brain on injection of heterologous brain. Witebsky pointed out that combination of brain emulsion with a foreign protein such as our pig serum often confused the result of the complement fixation reactions. This may serve to explain the ambiguous results which we obtained after only 4 weeks of inoculations.

Summary

It was found impossible to produce lesions in the brain of rats who had received injections of rabbit serum containing brain antibodies. The rabbits had received intraperitoneal injections of brain emulsion for 3 months, the technique corresponding to that employed by Masugi and others to produce experimental glomerulonephritis in animals. The result suggests that the demyelinization found in animals is probably not to be explained as due to the development of autogenous antibodies to brain or to some " cerebrotoxin " developed in the presence of brain lipoids.

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THE RÔLE OF POTASSIUM IN MYASTHENIA GRAVIS

BY

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IT has been shown that the affected muscles of patients suffering from myasthenia gravis contain more potassium than normal muscles (Cumings, 1939*b*), and that after the subcutaneous administration of prostigmin to myasthenic patients, the concentration of potassium in their muscles fell to a normal level, and also in one of the cases recorded in that paper the serum potassium was observed to rise as the muscle potassium fell. The present paper deals with a study of the fate of the potassium leaving the muscles.

Two patients with severe myasthenia affecting the muscles of the extremities as well as those of the neck were chosen, and for the period of the experiment were given a diet containing a known amount of potassium. The meals were prepared from weighed quantities of milk, sugar, apple, tomato, bread, butter, chicken, fish, egg, potato, cheese, and rice, and the amount of potassium was determined in each of these foods. Distilled water was used for all purposes. Although one of the two patients received a rather more liberal diet and one which at the same time contained a larger amount of potassium, neither patient received quite as much potassium in their food as a normal person would have done.

The urine was collected in three 4-hourly periods during the day, and one 12-hour period during the night (e.g. from 8 a.m. to 12 noon, 12 to 4 p.m., 4 to 8 p.m., and 8 p.m. to 8 a.m.). The stools were collected separately, charcoal being used to demarcate the periods. The volumes of each urine specimen, and the weights of the dried stools were recorded.

Neither patient received prostigmin or any other therapy for the first two experimental days, but on the third each was given prostigmin (mgm. 1) subcutaneously at the end of one of the 4-hourly periods (at 4 p.m.). Each day from the fourth day to the end of the experimental period both patients were given 3 gms. of potassium in the form of dipotassium hydrogen phosphate. The measure was washed out with distilled water after each dose and the washings administered to the patients.

* A grant was received from the research funds of the National Hospital towards part of the expenses.

TABLE 1.—SERUM POTASSIUM BEFORE AND AFTER PROSTIGMIN

	MISS M. (MYASTHENIA)	MRS. C. (MYASTHENIA)	A.B. (NORMAL)	K.S. (NORMAL)	R.N. (NORMAL)
Before first prostigmin injection	17·5 mgm. % of K	16·9 mgm. % of K	15·0 mgm. % of K	22·4 mgm. % of K	19·0 mgm. % of K
45 mins. after first prostigmin injection	23·3 ,, ,,	30·0 ,, ,,	15·2 ,, ,,	20·7 ,, ,,	18·3 ,, ,,
Before second prostigmin injection	29·2 ,, ,,	34·7 ,, ,,			
45 mins. after second prostigmin injection	39·1 ,, ,,	42·5 ,, ,,			

Further subcutaneous injections of prostigmin (mgm. 1) were given at 4 p.m. on the sixth day to one patient, and on the seventh day to the other patient, blood being taken before and 45 minutes after the injections. The experimental periods ended 40 hours after these last injections of prostigmin.

The potassium in the blood sera, urines, fæces, and foods was determined by the method previously used (Cumings, 1939*a*). The inorganic phosphate in the urine and fæces were estimated by Fiske and Subbarow's method (1925).

Results

Effect of Prostigmin on the Serum Potassium.—Table 1 shows the amounts of potassium found in the serum before and after the injection of prostigmin in the two patients and also in three normal subjects after one dose of prostigmin. The figures show that no alteration in serum potassium took place in the normal persons, but in both patients the administration of prostigmin was followed by an increase in the serum potassium, and that adding very large amounts of potassium to the diet raised the resting level of the serum potassium, but did not prevent the increase of that level after prostigmin. Clinically the effect of the prostigmin injection was excellent. The general muscular improvement was particularly rapid in the case of Miss M., who experienced considerable difficulty in swallowing.

Intake of Potassium.—Before considering the excretion of potassium, the daily intake of that substance is shown in Table 2. It is seen that apart from the first day there was a fairly constant amount of potassium in the food. It would seem unlikely therefore that the small variation in the potassium intake could account for the alterations in the level of serum potassium which followed the injection of prostigmin.

TABLE 2.—INTAKE OF POTASSIUM

DAY OF EXPERIMENT	MISS M.		MRS. C.	
	DIET	MEDICINE	DIET	MEDICINE
1	0·528 gm. of K.	—	0·539 gm. of K.	—
2	0·853 ,,	—	0·623 ,,	—
3	0·983 ,,	—	0·728 ,,	—
4	0·816 ,,	3·0 gm. of K.	0·784 ,,	3·0 gm. of K.
5	0·745 ,,	3·0 ,,	0·780 ,,	3·0 ,,
6	0·824 ,,	3·0 ,,	0·662 ,,	3·0 ,,
7	0·732 ,,	3·0 ,,	0·714 ,,	3·0 ,,
8	—	—	0·745 ,,	3·0 ,,
Total	5·481 ,,	12·0 ,,	5·575 ,,	15·0 ,,

Excretion of Potassium.—The excretion of potassium in the urine from the two patients is shown in Figs. 1 and 2. It will be seen that there was no increased excretion of potassium after the administration of prostigmin. A considerable increase did take place when the potassium was added to the diet. This increase, moreover, took place within 4 hours, so that any increase in the

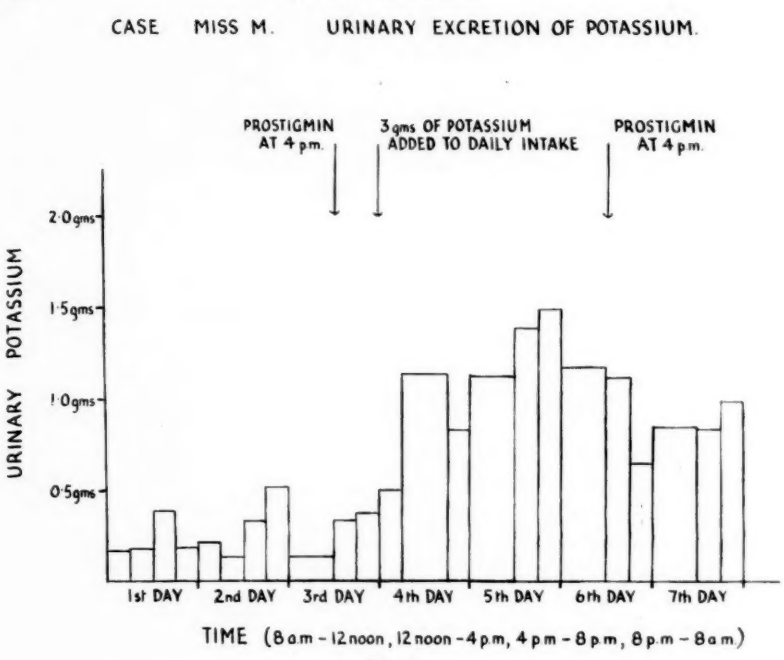
CASE MISS M. URINARY EXCRETION OF POTASSIUM.
PROSTIGMIN AT 4 p.m.
3 gms OF POTASSIUM ADDED TO DAILY INTAKE
PROSTIGMIN AT 4 p.m.
URINARY POTASSIUM
2·0 gms
1·5 gms
1·0 gms
0·5 gms
1st DAY
2nd DAY
3rd DAY
4th DAY
5th DAY
6th DAY
7th DAY
TIME (8 a.m - 12 noon, 12 noon - 4 p.m, 4 p.m - 8 p.m, 8 p.m - 8 a.m.)

Fig. 1.

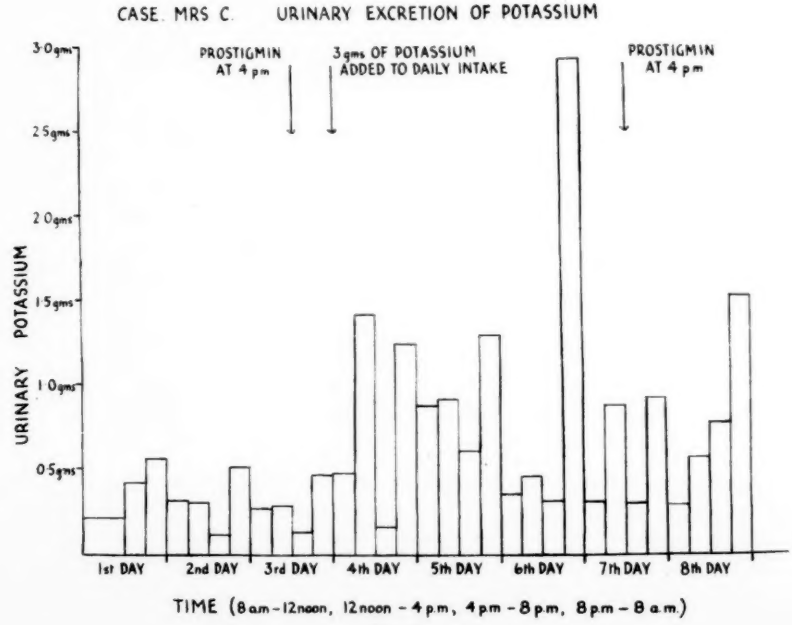
CASE. MRS C. URINARY EXCRETION OF POTASSIUM
PROSTIGMIN AT 4 p.m
3 gms OF POTASSIUM ADDED TO DAILY INTAKE
PROSTIGMIN AT 4 p.m
URINARY POTASSIUM
3·0 gms
2·5 gms
2·0 gms
1·5 gms
1·0 gms
0·5 gms
1st DAY
2nd DAY
3rd DAY
4th DAY
5th DAY
6th DAY
7th DAY
8th DAY
TIME (8 a.m - 12 noon, 12 noon - 4 p.m, 4 p.m - 8 p.m, 8 p.m - 8 a.m.)

Fig. 2.

urinary excretion of potassium consequent on the rise of serum potassium after prostigmin should have been seen within this same period.

The excretion of potassium in the stools is shown in Table 3. It is seen that no increased excretion of potassium has taken place at any time except on the fifth day of the experimental period in the case of Miss M. This is probably due to the slightly larger quantity of stool and because the patient was somewhat constipated for the first few days.

TABLE 3.—EXCRETION OF POTASSIUM IN STOOLS

DAY OF EXPERIMENT	MISS M.		MRS. C.	
	WEIGHT OF STOOLS (DRIED)	TOTAL AMOUNT OF K PRESENT	WEIGHT OF STOOLS (DRIED)	TOTAL AMOUNT OF K PRESENT
	GM.	GM.	GM.	GM.
1	—	—	—	—
2	—	—	47·5	0·751
3	—	—	—	—
4	13·5	0·309	39·2	0·786
5	27·0	1·118	—	—
6	14·5	0·423	—	—
7	30·0	0·636	20·8	0·870
8			—	—
9	40·0	0·895	26·0	0·711

Excretion of Inorganic Phosphate.—The figures for the excretion of inorganic phosphate in the urine and fæces from the two patients are given at the end of the paper, and it can be seen that no significant alterations have taken place as the result of the prostigmin injections.

Table 4 shows the potassium balances of the two patients over the whole period of the experiment.

TABLE 4.—POTASSIUM BALANCE

	MISS M.	MRS. C.
K intake in food	5·481 gm.	5·575 gm.
K intake in medicine	12·0 gm.	15·0 gm.
Total K intake	17·481 gm. for 7 days	20·575 gm. for 8 days
K output in urine	14·975 gm.	20·217 gm.
K output in fæces	3·381 gm.	3·118 gm.
Total K output	18·356 gm. for 7 days	23·335 gm. for 8 days
Balance	−0·875 gm. for 7 days −0·125 gm. per day	−2·760 gm. for 8 days −0·345 gm. per day

Discussion

One of the actions of prostigmin in myasthenia gravis is to liberate potassium from the affected muscles into the circulating blood. The total amount of this liberated potassium, which is in the blood, may be as much as 0·5 gm. (as calculated from the figures given in Table 1). It seemed possible that some of

this amount might have been found in the urine within a few hours after the administration of prostigmin. The urinary excretion of potassium, however, did not increase after prostigmin, Although the potassium in the diet varied somewhat from day to day, this variation did not cause any fluctuation of potassium excretion such that the sudden excretion of 0·5 gm. of potassium would not have been easily apparent. (Figs. 1 and 2, and Table 3.)

TABLE 5.—ACTION OF PROSTIGMIN UPON THE POTASSIUM CONTENT OF MUSCLE

TIME RELATIONSHIP	CLINICAL CONDITION AT THE TIME MUSCLE WAS REMOVED	K IN GM. PER CENT. OF DRY WEIGHT OF MUSCLE	K IN GM. PER CENT. OF WET WEIGHT OF MUSCLE	PHOSPHATE AS P IN GM. PER CENT. OF DRY WEIGHT OF MUSCLE	SERUM K MGM. PER CENT.
1.30 Prostigmin given. 3.30 Muscle and blood removed.	Normal except for very slight weakness of eye muscles.	1·23	0·32	0·92	27·4
5.15 Muscle and blood removed.	Marked weakness in many muscles.	1·89	0·44	1·12	20·4
5.20 Prostigmin given. 5.50 Muscle and blood removed.	No weakness	1·14	0·265	1·03	31·9

It would seem that the potassium liberated from the muscles into the blood must have remained for a time in the blood and then to have returned to the muscles. This seems the more probable since the potassium in the muscles rises again when the action of prostigmin wears off (*vide infra*). A patient, Mr. J., with severe myasthenia gravis was receiving four and sometimes five doses of prostigmin daily, and although each dose produced a rapid clinical improvement this improvement persisted for only about 4 hours. A biopsy was performed 2 hours after a dose of prostigmin ; $3\frac{3}{4}$ hours after this injection the patient became very weak and another sample of muscle was removed, after which prostigmin (mgm. 1) was again given. A third sample of muscle was taken $\frac{1}{2}$ hour later. Blood was taken each time muscle was removed. The potassium found in the three specimens of sera and in the three samples of muscle were estimated, and the results are seen in Table 5 together with the values for the phosphate found in the muscles. It is seen that the levels of potassium found in the second and third samples of muscle are in agreement with those recorded in my previous paper, and, moreover, that there was a slight increase in the amount of potassium found in the muscle 2 hours after prostigmin, as compared with the amount found after $\frac{1}{2}$ hour. It is also seen that the amount of potassium in the muscle increased considerably between 2 and $3\frac{3}{4}$ hours after prostigmin, during which time the clinical condition of the patient deteriorated. It therefore appears that the degree of muscular weakness is associated with the amount of potassium present in the muscle.

The fall in muscle potassium after the administration of prostigmin was accompanied by a small fall in the phosphate content.

The serum potassium was normal prior to prostigmin, it rose ½ hour after the injection, and had already begun to fall 2 hours later, at a time when the muscle potassium had begun to increase. This supports the view postulated above that some at least of the potassium liberated from the muscles after prostigmin is retained in the blood serum and not excreted in the urine, and that it returns to the muscles as the action of prostigmin wears off and the symptoms of myasthenia return.

Further work is now in progress to determine the factors controlling this return of potassium to the muscles, and the method by which prostigmin lowers the amount of potassium in the muscle.

INORGANIC PHOSPHATE EXCRETION

Urine Excretion (in mgm.)

DAY OF EXPERIMENT	TIME PERIOD	MISS M.		MRS. C.	
1	8 a.m.–12 noon		78·76		—
	12 noon–4 p.m.		68·6		87·70
	4 p.m.–8 p.m.		164·54		34·75
	8 p.m.–8 a.m.		336·76		288·29
2	8 a.m.–12 noon		93·18		124·98
	12 noon–4 p.m.		82·94		105·73
	4 p.m.–8 p.m.		41·33		69·54
	8 p.m.–8 a.m.		315·06		209·30
3	8 a.m.–12 noon		—		124·43
	12 noon–4 p.m.	Prostigmin mg. 1	75·07	Prostigmin mg. 1	116·28
	4 p.m.–8 p.m.	at 4 p.m.	146·64	at 4 p.m.	90·69
	8 p.m.–8 a.m.		342·4		356·40
4	8 a.m.–12 noon	K_2HPO_4 added to diet.	223·49	K_2HPO_4 added to diet.	139·78
	12 noon–4 p.m.		—		339·08
	4 p.m.–8 p.m.		438·75		119·39
	8 p.m.–8 a.m.		376·38		703·30
5	8 a.m.–12 noon		—		282·44
	12 noon–4 p.m.		306·55		330·40
	4 p.m.–8 p.m.		544·75		224·99
	8 p.m.–8 a.m.		472·16		631·80
6	8 a.m.–12 noon		—		172·10
	12 noon–4 p.m.		339·33		190·94
	4 p.m.–8 p.m.	Prostigmin mg. 1 at 4 p.m.	312·50		124·99
	8 p.m.–8 a.m.		316·80		1,031·97
7	8 a.m.–12 noon		—		126·34
	12 noon–4 p.m.		321·24	Prostigmin mgm.	287·62
	4 p.m.–8 p.m.		331·22	1 at 4 p.m.	188·67
	8 p.m.–8 a.m.		463·09		653·59
8	8 a.m.–12 noon		—		168·43
	12 noon–4 p.m.		—		193·39
	4 p.m.–8 p.m.		—		517·88
	8 p.m.–8 a.m.		—		312·40

Fæces Excretion

DAY OF EXPERIMENT STOOL PASSED	MISS M.	MRS. C.
1	—	—
2	—	0·696 gm.
3	—	—
4	0·437 gm.	0·738 gm.
5	0·611 gm.	—
6	0·216 gm.	—
7	0·657 gm.	0·601 gm.
8		—
9	1·184 gm.	0·455 gm.

Summary

Potassium balance experiments were conducted on two patients with myasthenia gravis and the effect of prostigmin on the excretion of potassium studied.

It has been shown that although the muscles liberate potassium into the blood serum after the injection of prostigmin, there is no increased urinary excretion of potassium. The potassium appears to be retained in the blood and to return to the muscles as the weakness of the muscles reappears.

My sincere thanks are due to Dr. D. Brinton and Dr. J. St. C. Elkington for allowing me to utilize the two patients on whom potassium balances were done at the National Hospital, and to the co-operation of the Nursing Staff, to Dr. McCartan of Hurstwood Park Hospital, Haywards Heath, to Mr. Harvey Jackson, F.R.C.S., and to Mr. R. Nunn, B.Sc., for his help in the estimations.

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ATROPHY OF THE THALAMUS IN A CASE OF ACQUIRED HEMIPLEGIA ASSOCIATED WITH DIFFUSE PORENCEPHALY AND SCLEROSIS OF THE LEFT CEREBRAL HEMISPHERE

BY

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(RECEIVED 1ST DECEMBER, 1939)

THE following case is reported both on account of its unusual pathological features and the opportunity it affords of studying thalamic atrophy in an example of what is for all practical purposes the equivalent of an experimental hemidecortication in a human subject. In recent years a considerable amount of experimental work has been completed on the study of thalamo-cortical connections in lower mammals. This work has demonstrated that the projection of different thalamic nuclei on to different areas of the cortex is more precise and also more extensive than had been generally supposed. In experimental animals, the degree to which thalamic nuclei are functionally dependencies of the cortex has been assessed in some cases by the study of cell degeneration in the thalamus following complete, or almost complete, hemidecortication.

Since in the present case the pathological condition has led to a destruction of the cortex while the basal ganglia have been left intact, it also permits of a differentiation between thalamo-cortical connections, and possible thalamo-striate connections which may exist (and which have been described) in respect of some of the nuclear elements of the thalamus.

Clinical History

M. B., a girl aged thirteen years, was first admitted when eight years old to the wards of the London Hospital on 8th August, 1933, under the care of Dr. Donald Hunter, to whom we are indebted for the following clinical notes.

She had complained of occasional headaches during the preceding three weeks. On the day of admission a sudden attack of vomiting was followed by convulsions affecting the right side of the body, and unconsciousness. She had previously been healthy. There was no history of epilepsy or of other neurological diseases in the family. One sister, aged four and a half years, was alive and well.

On Examination.—She was obviously ill and in a state of cerebral irritability.

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Temperature 105·5° F. Pulse 150. The fundi appeared normal. There was conjugate deviation of both eyes to the right and nystagmus. The reactions of the pupils were normal. There were clonic convulsions of the right hand and right face. The knee and ankle jerks were absent and an extensor plantar response was obtained on the right side. No abnormal physical signs were found in the chest or abdomen.

On 9th August a right hemiplegia and right facial paralysis developed. Some evidence of infection of the post-nasal region and of the left middle ear was found, but needling of the left temporal lobe through a trephine hole yielded cerebro-spinal fluid and thus it was concluded that no abscess was present. On 10th August there was slight neck rigidity and Kernig's sign was positive on the right side. The left arm and leg moved in response to pin-prick.

A later note states that a flaccid paralysis of the right arm and leg with increased tendon reflexes persisted. The general condition improved and by 28th August " she was able to recite nursery rhymes." (This may be taken to imply that there had been some impairment of speech at an earlier stage.) On 8th September it is noted that she appeared well and happy, talked freely, and was normal mentally. On 16th September a slight degree of apraxia was recorded and a greater degree of spasticity of the right limbs. She was able to kick with the right lower limb and to move it fairly freely. Movements of the right upper limb were beginning and there was less weakness of the right face. Both plantar reflexes were extensor, but no other abnormal signs were found in the left leg. On 23rd October the changes in the nervous system had become stationary and she was discharged to a convalescent home wearing a surgical boot.

The following were the findings of the laboratory investigations.

Cerebro-spinal Fluid.—9th August (a) by lumbar puncture : clear fluid at 180 mm. pressure ; 0·035 per cent. of protein ; 0·73 per cent. of chlorides ; 53 cells per cmm., mostly lymphocytes. Cultures sterile. Wassermann reaction negative.

(b) From lateral ventricle : 0·035 per cent. of protein : no excess of white cells.

10th August. Lumbar puncture : protein, 0·045 per cent. ; 96 cells per cmm., 60 per cent. lymphocytes and 40 per cent. neutrophil leucocytes.

Urine.—9th August. Albumin, a cloud ; a few red blood-corpuscles, occasional leucocytes and epithelial cells in deposit.

On 18th May, 1936, the child was re-admitted on account of attacks of unconsciousness lasting about 30 seconds. These had started soon after her discharge from hospital, occurring at first about twice a week and then becoming more frequent. There was no headache. On examination it was found that intelligence and speech were normal. There was no pyrexia. A right homonymous hemianopia was recorded, but the notes do not contain charts of the visual fields. Weakness of the right face was apparent during voluntary movements. The tongue was protruded slightly to the right. The right upper limb showed diminished power, hypertonia, and increased tendon reflexes without wasting. The abdominal reflexes were absent on the right, present on the left. The right lower limb showed 2·5 cm. of shortening with contracture of the Achilles tendon, spasticity, and diminished power. The deep reflexes were exaggerated ; there were patellar and ankle clonus and an extensor plantar response on the right. No sensory disturbance was detected.

Several fits were observed while she was in hospital. These came on suddenly without an aura. In them she cried and fell to the left, remaining unconscious for about 30 seconds. Afterwards she was dazed for a short time, and this was followed by involuntary jerky movements of the right arm and leg. There was no incontinence of urine nor biting of the tongue. The attacks continued and, when on 15th July, 1938, she was again re-admitted, she was in status epilepticus. Two weeks before this she had had an attack of diarrhœa and vomiting. Eight days before admission convulsions had become almost continuous. Examination on this admission revealed the following

signs : There was twitching of the eyelids, mouth, right hand and leg, followed by tonic and clonic contractions. Sedative drugs were ineffective. Unconsciousness persisted, and after further fits she died on 17th July, 1938.

The brain was injected with formaldehyde through the right carotid artery on the day of death. The necropsy was performed on the following day, and we are indebted to Dr. J. R. Gilmour for the following summary.

Summary of Necropsy

Status Epilepticus. Atrophy and Sclerosis of Left Cerebrum.—Severe parenchymatous degeneration of myocardium. Slight general atheroma. Broncho-pneumonic consolidation and almost complete collapse of lower lobe of right lung. Hæmorrhage between posterior common ligament and sides of lower thoracic and lumbar vertebræ. Moderate fatty degeneration of liver. Slight albuminous degeneration of kidneys. Middle ears and accessory nasal sinuses normal. Slight generalized pigmentation of skin. Healed trephine wound in skull. Right lower limb 2 cm. shorter than left ; right upper limb 1·5 cm. shorter than left. A well-nourished, otherwise well-developed, girl. Height 160 cm. Weight 48·65 kg.

Pathology of Central Nervous System

Macroscopic Examination.—The left cerebral hemisphere was greatly atrophied (Fig. 1), all areas being affected except the anterior two-thirds of the cingulate gyrus, the uncus and adjacent medial part of the hippocampus, including the dentate gyrus, a narrow strip of the inferior temporal convolution, the lips of the calcarine fissure, and the terminal 1·5 cm. of the occipital pole. Over these parts of the hemisphere the leptomeninges were thin and of normal transparency ; elsewhere they appeared cloudy and greyish-white, and in places were thrown into irregular folds (Fig. 1). The atrophied convolutions felt soft and spongy. The right cerebral hemisphere appeared normal. The right cerebellar hemisphere was slightly smaller than the left due to a generalized but unequal atrophy of the folia.

Both internal carotid arteries were of equal size and of normal translucency ; the main cerebral arteries were patent and of normal appearance on both sides.

On section the cortex of the left cerebrum, except in the unaffected areas mentioned, was found to be replaced by a thin layer of soft, grey, spongy tissue composed of delicate trabeculæ enclosing empty spaces mostly less than 0·1 cm. diameter but occasionally measuring up to 0·5 cm. diameter (Figs. 2, 3). Deep to this porous layer and throughout the hemisphere the white matter was grey and of a curious rubbery consistency suggestive of wash-leather. In the left paracentral lobule the cortex was not porous, but its outline was blurred and the white matter tough and rubbery as elsewhere. In addition there were occasional areas in the more grossly affected parts of the convexity where the cortex was homogeneous and yellowish-grey ; such foci tended to occupy the depths of the sulci.

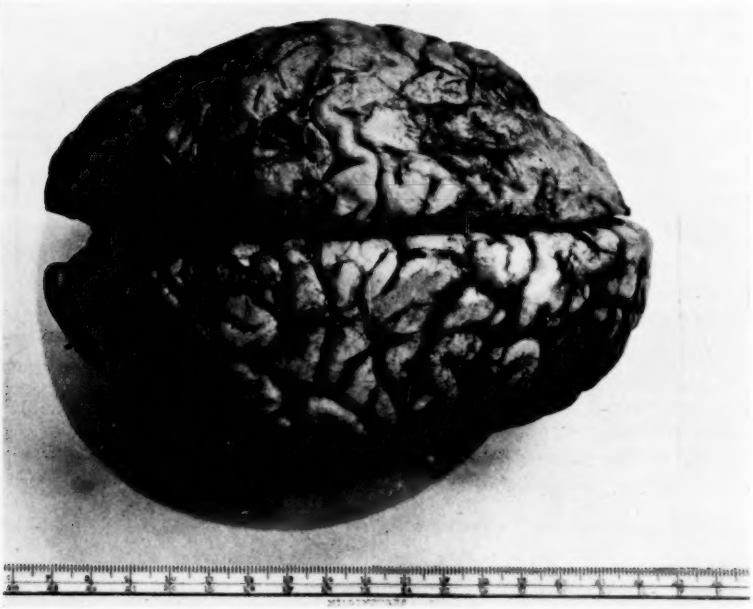

Fig. 1.—Dorsal view of brain showing atrophy of left cerebral hemisphere. Note thickening and corrugation of leptomeninges.

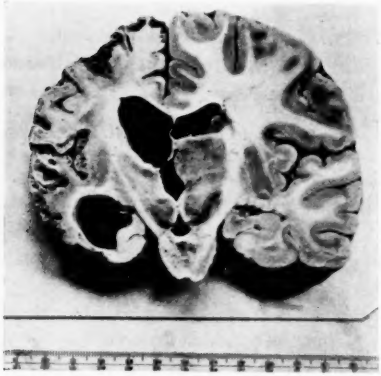

Fig. 2.—Section of the brain at the level of the middle of the thalamus. Note the shrinkage of the thalamus on the left side. Note, also, that the whole extent of the cortex on the left side has undergone complete pathological destruction with the exception of the gyrus cinguli, the hippocampal formation, the hippocampal gyrus, and a narrow strip of the inferior temporal convolution.

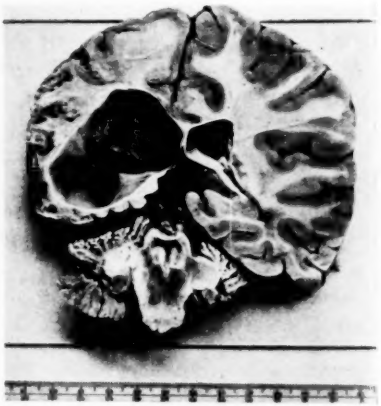

Fig. 3.—Section of the brain behind the level of the thalamus. Note that the upper end of the central convolutions remains partly intact (in macroscopical appearance), and that the visual cortex has been stretched out to form a thin layer in the medial wall of the dilated posterior horn of the lateral ventricle. The choroid plexus is adherent to its lateral wall.

The left lateral ventricle was greatly dilated (Fig. 3). Its ependyma was everywhere smooth and glistening except where a tag of the left choroid plexus had become adherent to the lateral wall in the temporo-occipital region (Fig. 3). This choroid plexus appeared in other respects normal. The corpus callosum was greatly atrophied, measuring from 0·25 cm. to 0·3 cm. in thickness. There was also great atrophy of the left optic thalamus, details of which are separately described below. The left internal capsule and crus were considerably wasted.

Spinal Cord.—There was no obvious alteration in structure ; the anterior spinal roots and horns appeared equal and normal.

Microscopic Examination

Methods.—Blocks were selected from representative parts of the central nervous system both for paraffin and for frozen sections. Paraffin sections were stained with Ehrlich's hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, Weigert's fuchselin and neutral red, phosphotungstic-acid hæmatoxylin, Roussy and Lhermitte's modification of Nissl's method and the Loyez hæmatoxylin method for myelin. Sections cut on the freezing microtome were stained with Scharlach R. for fatty substances, Spielmeyer's method for myelin, Bielschowsky's and Rio-Hortega's methods for neurofibrils and Penfield's modification for oligodendroglia and microglia.

Left Cerebral Hemisphere.—The leptomeninges over the left cerebrum are thickened wherever convolutional atrophy is present. This thickening appears to be due to redundancy of the meninges since there is no obvious increase of fibrous tissue, and the texture is spongy. In places there is sparse infiltration of the deep surface of the arachnoid membrane and of the pia immediately over the cortex by small lymphocytes, occasional neutrophil leucocytes, and mononuclear cells. The blood-vessels everywhere appear normal with the exception of a single arteriole in the frontal region in which slight focal hypertrophy of the intima has produced a crescentic thickening. The adjacent media is normal.

The cortex is almost everywhere greatly atrophied, being replaced by a spongy tissue in which anastomosing trabeculæ of densely felted neuroglial fibrils enclose spaces of varying size and shape (Fig. 4). These spaces sometimes contain a few foam cells and, more rarely, small lymphocytes. In the most severely affected areas all the neurones have disappeared ; occasionally they persist as "fossils" encrusted with iron salts (Fig. 5). In the less severely affected parts, for example the cingulate gyrus and the visual cortex, the neurones are well preserved. Transitional stages can be distinguished in passing from these areas towards those that have undergone atrophy ; in these the neurones show progressively greater degrees of distortion of shape, eccentricity of the nucleus, and margination and chromatolysis of Nissl substance. Accompanying these changes is a progressive gliosis, shown by the presence in silver preparations of astroblastic and binucleated forms, and stages in the development of porous areas (Fig. 6). In the intact and less affected areas the microglial cells are either normal or show slight amœboid swelling and occasional rod forms. The oligodendroglial cells likewise are normal or slightly swollen. In the more

Fig. 4.—Left occipital cortex showing replacement of cortex by dense glial feltwork enclosing irregular spaces. The deep border of the cortex is represented by the larger oval space to left of centre. Phosphotungstic acid hæmatoxylin. ×93.

Fig. 5.—Left motor cortex showing pyramidal cells encrusted with iron salts. Amongst them are many similarly encrusted fragments of dendrites. Rio-Hortega's silver carbonate for neurofibrils. ×490.

severely affected parts the microglial cells are scarce ; amœboid forms are occasionally present in the walls of the cavities, and compound granular cŏrpuscles containing globules of fat are often present singly or in small groups within the cavities. The oligodendroglial cells are scanty ; in strong contrast to those in the more normal areas and in the right cerebrum they are invariably devoid of processes, greatly atrophied, and contain shrunken pyknotic nuclei.

Silver preparations to demonstrate connective tissue show a dense network

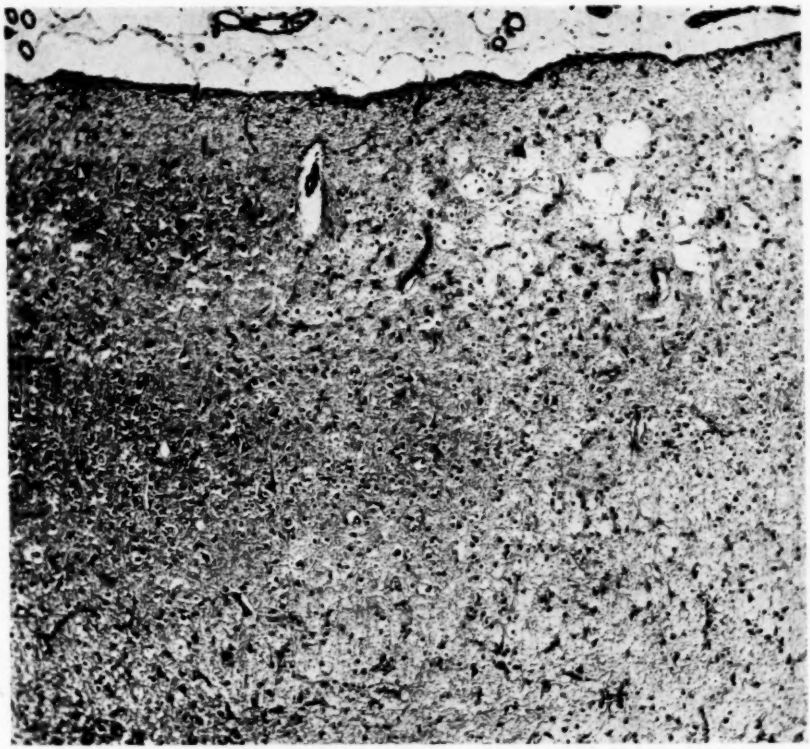

Fig. 6.—Cortex near area striata showing, on right, early stages in formation of cavities with disappearance of neurones. Phosphotungstic acid hæmatoxylin. ×76.

of blood-vessels with slightly thickened walls throughout the atrophied parts of the cortex. There is, however, no histological evidence of any new formation of vessels : the appearances suggest that their prominence is due to condensation secondary to atrophy.

In the white matter there is an almost complete loss of myelin beneath affected parts of the cortex accompanied by a dense and relatively acellular gliosis (Figs. 7, 8). The few surviving myelin sheaths frequently show ballooning and fragmentation. Beneath unaffected parts of the cortex, such as the

area striata, the white matter appears normal. The transition between the normal and abnormal parts is gradual and it is remarkable that, in the transi-

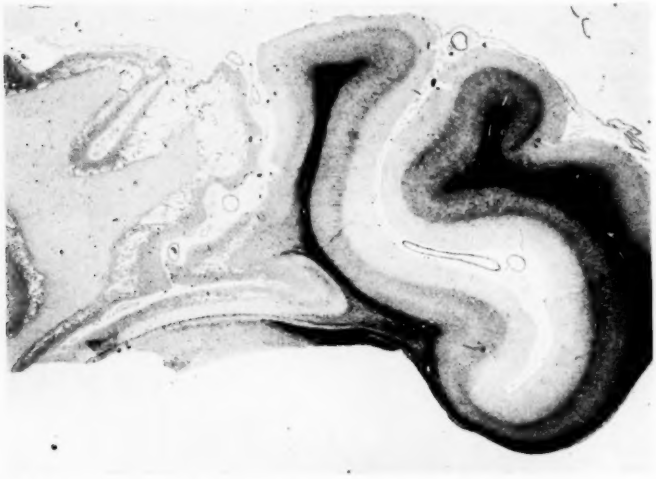

Fig. 7.—Left occipital cortex showing preservation of area striata on right. Cortical destruction and complete demyelination of neighbouring gyrus. Loyez' hæmatoxylin. ×4·2.

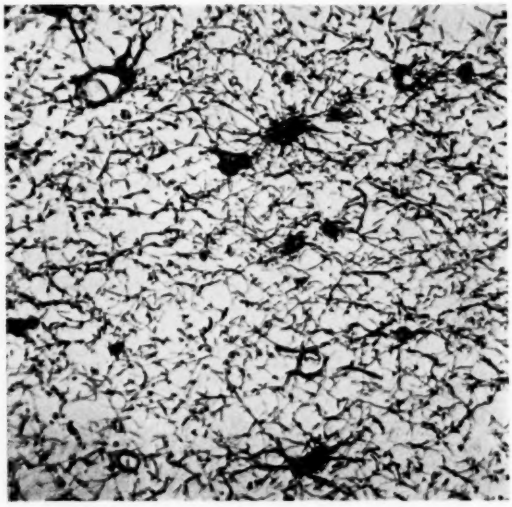

Fig. 8.—Subcortical tissue from left occipital lobe showing replacement of white matter by astrocytes. Two binucleated cells are present near centre of field. Phosphotungstic acid hæmatoxylin. ×380.

tional areas examined, the changes in the white matter appear rather more advanced than those in the overlying cortex.

The character of the gliosis differs from that in the cortex both in texture and in the form of the cells. In the cortex densely felted bundles of piloid astrocytes are present in all severely affected areas ; in the white matter the interlacing neuroglial fibres are less dense and the cells are stellate. Frequently they are binucleate (Fig. 8). Compound granular corpuscles containing fatty substances are distributed rather sparsely and irregularly in the affected white matter ; they sometimes form cuffs in the Virchow-Robin spaces of the blood-vessels. The scarcity of oligodendroglial cells is more remarkable here than in the cortex ; all show advanced atrophy as already described.

Sections through the site of attachment of the choroid plexus to the lateral wall of the ventricle in the parieto-occipital region show fibrous union between the stroma of the plexus and the ependyma. There is no inflammatory reaction in the adjacent tissues. The choroid plexus appears normal apart from the presence of a few calcospherites in its stroma.

Representative sections from different parts of the right cerebral hemisphere show no histological abnormality apart from the occasional presence of small lymphocytes and sparser neutrophil leucocytes in the leptomeninges.

A similar sparse cellular infiltration is present in the leptomeninges over the cerebellum. The left cerebellar hemisphere appears normal. All folia of the right cerebellar hemisphere are slightly but unequally atrophied. The atrophy is accompanied by a partial, sometimes marked, loss of both Purkinje cells and granule cells and by a gliosis due to proliferation of the Bergmann cells. There is no demonstrable change in the white matter.

The spinal cord is normal apart from a descending pyramidal degeneration on the right side.

Changes in the Left Optic Thalamus

Before describing the distribution of the cell atrophy in the thalamus, it is desirable to refer again to the precise extent of the cortical destruction. As already noted, almost all the cortex has been completely disorganized by the pathological process, and even deep-lying tracts of cortex, such as the whole of the insular area, have been involved. Certain regions, however, have escaped destruction. The visual striate cortex, it is interesting to note, has been left intact so far as its intrinsic structure is concerned (Fig. 7). Sections of this area, stained with toluidin blue, show the various cell-laminæ to be quite well defined, each lamina containing its characteristic cells in an apparently normal condition. It is not possible to affirm that no cell atrophy at all has occurred in the visual cortex, but, if it has occurred, it is too slight to be detected by any change in cytoarchitectural appearance.

A strip of the cingulate gyrus which is in immediate relation to the corpus callosum has also escaped complete destruction (Fig. 2). Sections have shown, however, that the cytoarchitecture of this cortex is not normal, for, while numbers of well-formed pyramidal cells are still present, there is evidently a general atrophy affecting all the cell layers. The immediately subjacent white matter, also, shows a marked gliosis.

On the convex surface of the brain, the whole extent of the cortex has been destroyed with the exception of a small portion of the upper end of the central convolutions (Fig. 3). Here, as in the cingulate gyrus, there are marked atrophic changes. As in the case of the striate cortex, the distribution of the incompletely involved cortex in the gyrus cinguli and the central convolutions suggests a relation to blood-supply, for these areas of the cortex are vascularized by the main branches of the anterior cerebral artery.

The only other portions of the cortex to escape involvement are the dentate gyrus, the hippocampus, the hippocampal gyrus, and a narrow strip of the inferior temporal convolution. Like the striate area, these cortical structures are supplied by the posterior cerebral artery.

In summary, it may be noted that all that part of the cortex comprising the vascular territory of the left middle cerebral artery has undergone complete disorganization. The same process has also extended in some degree into the territories of supply of the anterior and posterior cerebral arteries except along the distribution of the main cortical branches of these vessels.

Macroscopically, the left thalamus is seen in sections to be considerably shrunken in size (Fig. 2). Spaced serial sections of the whole of the thalamus of both sides were prepared, and stained with toluidin blue. These were systematically studied in order to determine the extent of the cellular atrophy which had occurred. The results of this study may most conveniently be described by reference to individual nuclear elements.

Anterior Nucleus—This element (which corresponds to the nucleus antero-ventralis of lower mammals) has undergone complete degeneration with replacement of the cells by a dense gliosis, except in the rostral half of the nucleus where there is a small circumscribed cluster of apparently normal cells in its medio-ventral part. In the caudal half of the nucleus no normal cells could be found. It has now been well established that the nucleus antero-ventralis projects on to the gyrus cinguli (Le Gros Clark and Boggon, 1932), and it undergoes complete atrophy following experimental hemidecortication in the chimpanzee (Walker, 1938). The persistence of a few cells in the present case is almost certainly related to the fact that a strip of the cingulate gyrus has escaped complete destruction.

Ventral and Lateral Nuclei—These elements of the thalamus have undergone practically complete degeneration. In rostral planes, occasional isolated and normal cells are seen at the ventro-lateral margin of the ventral nucleus, but it is difficult to determine whether these belong to the ventral nucleus proper, or to that part of the nucleus reticularis which is in immediate relation to it. In the caudal part of the thalamus, a slender strand of scattered cells extends dorso-laterally through the region of the ventral nucleus (Figs. 9, 10). This line of cells becomes even less distinct more posteriorly, and is finally reduced to odd scattered cells in the same region which are not easy to find except by careful scrutiny of the sections. Apart from these exceptions, and the presence of a very occasional cell to be found by searching over wide fields, all the neurones of the lateral and ventral nuclei have disappeared and are replaced by an exceptionally dense gliosis. It is reasonable to assume that

the persistence of some of the cells is related to the fact that a small portion of the central gyri has escaped complete destruction by the pathological process.

Following hemidecortication in the chimpanzee and monkey, Walker (1935, 1938) found the rostral extremity of the ventral nuclear mass free from degeneration, suggesting that in these animals this element (nucleus ventralis anterior) does not project on to the cerebral cortex. In the decorticated cat, Waller (1938) found the persistence of normal cells in the medial part of the anterior ventral nucleus, while, in similar experiments, Bard and Rioch (1937)

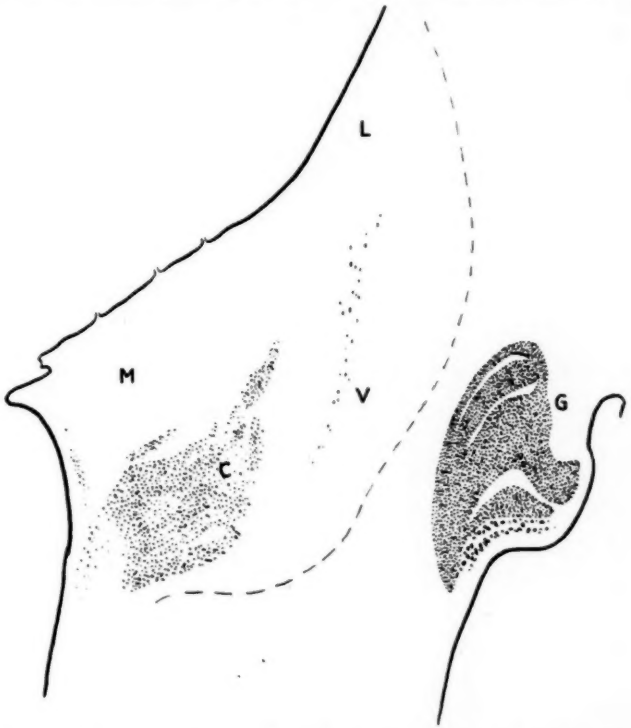

Fig. 9.—Drawing of a section through the thalamus at the level of the anterior part of the centre median nucleus (traced with a projection apparatus). C. Centre median nucleus. G. Lateral geniculate body. L. Lateral nucleus. M. Medial nucleus. V. Ventral nucleus. ×5.

found the nucleus almost completely degenerated, with only occasional normal cells persisting. In the present case, the cells occupying the topographical position of the nucleus ventralis anterior have apparently undergone total degeneration, and it may be inferred, therefore, that in the human thalamus the whole antero-posterior extent of the ventral nuclear mass is entirely concerned with the projection of ascending fibres to the cortex.

Medial Nucleus (*Nucleus Dorso-medialis of Lower Mammals.*)—This element shows complete degeneration, except only for the appearance in odd sections of a very occasional isolated cell, or a cluster of cells (up to seven or

eight), which can be found by careful searching. It is now established that the medial nucleus projects on to the prefrontal cortical fields. While in lower mammals this is certainly true for most of the cells of the medial nucleus except for some larger neurones at its medial margin, the present case suggests that in the human brain it applies to the entire nucleus.

Pulvinar.—No normal nerve cells could be found in any part of the pulvinar —everywhere the normal cytoarchitecture is replaced by a dense gliosis.

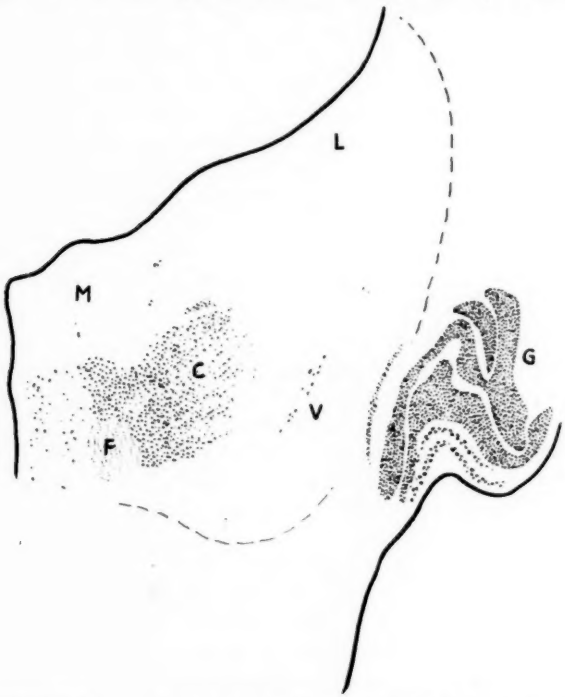

Fig. 10.—Drawing of a section through the thalamus at the level of the posterior part of the centre median nucleus (traced with a projection apparatus). F. Fasciculus retroflexus. Other lettering as in previous figure. ×5.

Experiments involving isolated cortical lesions have shown that the pulvinar projects mainly on to the posterior parietal cortex (Le Gros Clark and Northfield, 1937), and the element has been shown by Walker to undergo complete degeneration following decortication in the monkey and chimpanzee.

Centre Median Nucleus.—This thalamic element persists apparently unchanged. Surrounded by areas of total cell atrophy and conspicuous gliosis, it stands out in toluidin blue sections quite sharply defined (Figs. 9, 10, 11). Its cells stain normally, and, so far as can be judged by direct examination of the sections and comparison with the opposite thalamus, they show their normal density. The ground-substance of the nucleus, however, shows a slight degree of gliosis which may be related to the degeneration of fibres of

passage, or of descending cortical connections. It is, of course, not possible to affirm that none of the cells of the centre median nucleus have undergone degeneration ; it is possible to say, however, that certainly the great majority, and probably all, of them remain intact.

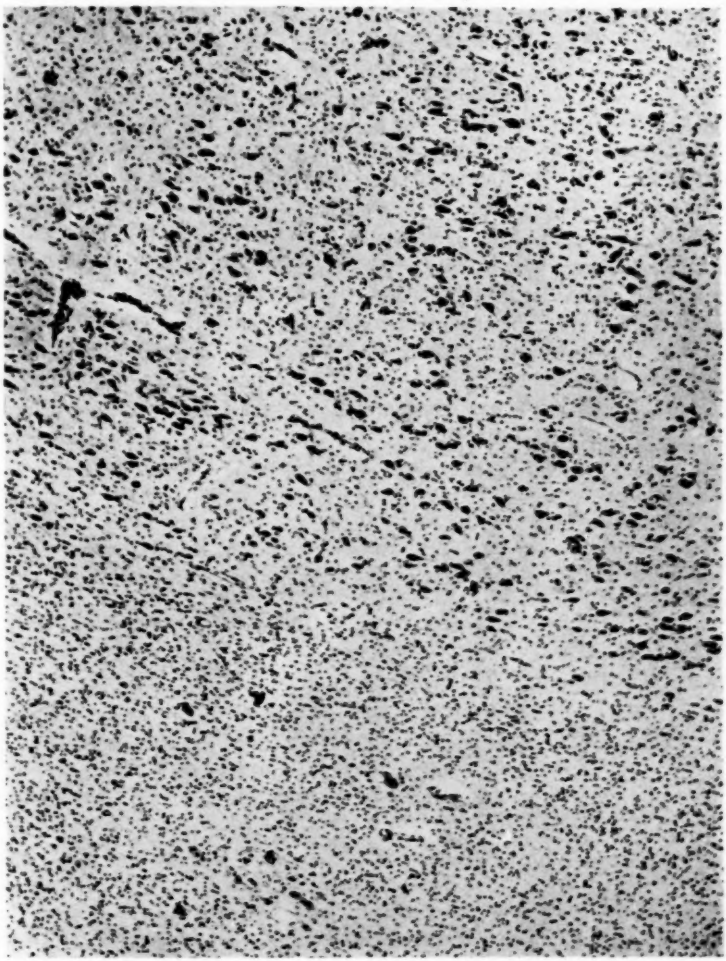

Fig. 11.—Microphotograph of a section showing (above) a part of the centre median nucleus with intact cells, and (below) the region of the ventral nucleus in which the cells have disappeared and have been replaced by a dense gliosis. ×55.

The persistence of the centre median nucleus in the midst of degenerated areas following hemidecortication has been noted by Walker in the chimpanzee and monkey, whence it appears that this element does not send any projection fibres to the cerebral cortex. On the other hand, its connections remain quite

obscure. In a pathological case reported recently (Le Gros Clark and Ritchie Russell, 1939), in which a vascular lesion had isolated the insular cortex, the centre median nucleus was found to have undergone practically complete degeneration, while most of the adjacent nuclei were unaffected. This observation suggested the possibility that the centre median nucleus may project on to the insular cortex and, in order to test this, the insular area in a macaque monkey was completely destroyed by the method of devascularization. In this experiment, however, the nucleus remained intact, and it is quite apparent from this and from the previous experiments of other authors that in the monkey it is not connected with the insula. On the other hand, the possibility still remained that it might do so in the human brain in which the insula shows the development of new cytoarchitectural areas. This possibility is now ruled out by the present case.

The suggestion that the centre median nucleus sends its efferent fibres to the corpus striatum has been entertained by a number of authorities. More recently, some experimental evidence has been adduced in support of this view. Walker (1938*a*) found complete degeneration of the nucleus in a monkey after decortication with marked damage to the basal ganglia, and, since in other experiments in which the caudate nucleus and putamen only had been partly destroyed the element remained normal, he suggested that it probably projects on to the globus pallidus portion of the basal ganglia. In the pathological case to which reference has just been made, however, the globus pallidus was intact and the vascular lesion had only involved a relatively small portion of the putamen of the lentiform nucleus. Since this limited striatal lesion was judged to be hardly adequate to account for the practically complete atrophy of the centre median nucleus, the efferent connections of the latter still remain in doubt.

Dr. J. G. Greenfield has recently permitted one of us to examine sections of the thalamus from a case of Kernicterus lately described (FitzGerald, Greenfield, and Kounine, 1939). In this case (No. 1) the ganglion cells of the globus pallidus "had almost completely disappeared, only sparse shrunken cells remaining." Nevertheless, the sections show that the centre median nucleus appears quite normal in its nerve-cells and its glial content.

Lateral Geniculate Body.—The cells of all the laminæ of this visual centre appear to be completely normal. This is somewhat surprising considering the degree to which the cortex of the occipital lobe has been stretched out to a thin layer in the wall of the dilated lateral ventricle. On the other hand, the fact that the lateral geniculate body remains normal in structure, while all parts of the pulvinar have undergone complete degeneration, is in harmony with the observation that normal striate cortex is rather sharply circumscribed by completely degenerated cortex, for it is known from experimental work that some elements of the pulvinar project on to the peristriate area which immediately surrounds the visual cortex (Le Gros Clark and Northfield, 1939).

Medial Geniculate Body.—This nucleus has undergone complete degeneration as the result of the destruction of the audito-sensory cortex.

Nuclei of the Mid-line.—Throughout the thalamus on the affected side,

a thin zone of small nerve-cells persists in a subependymal position along the wall of the third ventricle. These cells are surprisingly few in number as compared with the cells of the mid-line nuclei which are reported to remain intact in lower mammals after decortication.

Intralaminar Nuclei.—In lower mammals, the main thalamic nuclei are outlined by strands of cells occupying the position of medullary laminæ, and these intralaminar nuclei persist after decortication. Some of them are well enough defined anatomically to merit description as separate nuclear elements of the thalamus. In the human brain they are less conspicuous, and in the present case they are not evident at all. There is a complete absence of cells corresponding in position to the nucleus paracentralis and the nucleus centralis lateralis of lower mammals, for instance. From the rostral end of the centre median nucleus a strand of cells extends for a short distance dorso-laterally into the lower part of the medial medullary lamina (Fig. 9), but except for this extension there is no persistence of the intralaminar nuclei.

Nucleus Reticularis.—This thin layer of cells has apparently undergone complete degeneration except possibly in rostral planes where (as already noted) some normal cells at the lateral margin of the ventral nucleus are to be found intact.

Comment

In this case an acquired hemiplegia in childhood is correlated pathologically with a conspicuous degree of atrophy and porencephaly of the left cerebral cortex and with advanced demyelination and gliosis of the white matter of that hemisphere. Although infantile hemiplegia has usually been ascribed to a congenital defect or to birth trauma, it is generally recognized that post-natal examples also occur. Most of these are due to circulatory disturbances such as sinus thrombosis, or embolism secondary to infective endocarditis. Such disturbances are ruled out in the present case both by the observations at necropsy and the morbid anatomy of the brain. An infective origin in certain of these cases is postulated by Wohlwill (1936) who suggests that, when the onset is acute and accompanied by high fever, the condition should be regarded as a " genuine encephalitis." The clinical features of this type are described by Taylor (1905) as follows : " A child hitherto healthy and without hereditary stigmata becomes ill without any apparent cause, between the ages of one month and six years. The early symptoms are severe, and consist of fever, convulsions, often vomiting and coma. These symptoms persist from twenty-four hours to a week ; and towards the end of the period, as the general condition improves, hemiplegia is noticed to come on, first in the face, then in the arm, and lastly in the leg. The hemiplegia becomes severe and the limbs remain flaccid for some days, after which the flaccidity begins to disappear and the limbs become spastic. In some cases the paralysis disappears completely. In most cases a greater or less degree of paralysis or perversity of movement remains." The pathology of this type of acquired hemiplegia is, however, still obscure. Strümpell (1885) claimed that it represented the cerebral form of infantile poliomyelitis, but the existence of such a condition is now disputed. Pette

(1936) declares that, in a wide experience, he has never seen a case and considers it wiser to assume that it does not exist. Grinker (1937) considers that this so-called Strümpell-Leichtenstern type should be regarded as an acute syndrome, the ætiological factors of which may be varied.

While infantile poliomyelitis cannot be absolutely ruled out in the present case, the absence of any histological changes in the anterior horn cells is against this diagnosis. The clinical history and results of examination of the cerebrospinal fluid point strongly, however, to an initial acute inflammation of the central nervous system. The relatively small number of cells in the lumbar spinal fluid suggests that the initial condition was an encephalitis rather than a meningitis. The ætiological agent, however, has not been demonstrated. The histological examination, while disclosing an unusual kind of cerebral destruction, yielded no information bearing on this point. The changes in the white matter of the left hemisphere bore a close resemblance to those in Schilder's encephalitis, but the condition as a whole differs strongly from this disease in the conspicuous involvement of the cortex, the unilateral involvement of the brain and absence of any evidence of progression from the occipital to the frontal lobe. In the involvement of the cortex and the development of porous areas there is perhaps a stronger resemblance to certain examples of diffuse progressive cerebral sclerosis in infants (Russell and Tallerman, 1937).

Amongst cases reported in the literature the nearest approach to the present one was found in the two examples described by Bielschowsky (1917–18). In his first case there was an acute onset at the age of five years, accompanied by fever, convulsions, and a skin rash, and followed by hemiplegia. Epileptic convulsions persisted during the following eighteen years and the patient died, an imbecile, at the age of 23. In his second case the initial attack, characterized by severe convulsions and loss of consciousness, occurred at 6 years ; it was followed by weakness of the right side and loss of speech. Later there was an improvement in speech but the hemiplegia persisted. Epileptiform convulsions and deterioration of intelligence became pronounced and the patient died in post-epileptic coma at the age of 14. In both these cases the brain showed a unilateral atrophy similar to that described in our present case except that cortical destruction was less severe and the sub-cortical white matter showed neither demyelination nor gliosis. The lateral ventricle on the atrophied side was grossly dilated as in the present case. This dilatation obviously differs from a true internal hydrocephalus in that no obstruction is present : it is the result of atrophy with retraction of the tissues. A bilateral dilatation is similarly found in examples of progressive cerebral sclerosis of infants. Bielschowsky's cases again resembled ours in the preservation of the area striata and lateral geniculate bodies, and in the well-marked atrophy of the optic thalamus.

With respect to the thalamic atrophy in our case it may be said, in general, that the only elements which persist undegenerated are the lateral geniculate body, the centre median nucleus, and a narrow subependymal zone of small cells.* The lateral geniculate body in the primates is known to project entirely

* The elements of the epithalamus (habenular and paratænial nuclei) are not considered here. These elements are not affected by the degeneration which involves the thalamus proper.

on to the visual cortex, and in the present case this cortical area had escaped pathological destruction. The occasional normal cells which are still to be found in the anterior, ventral, and other nuclear elements (to which reference has already been made) almost certainly owe their survival to incomplete destruction of the cortical areas to which they are related. The conclusion naturally follows that every nuclear element of the human thalamus is entirely concerned with the projection of impulses on to some part of the cerebral cortex, with the exception only of the centre median nucleus and the subependymal zone of cells. This conclusion is based on the assumption that the atrophy of the cells is the direct result of the interruption by the cortical destruction of their axonal processes. The possibility that the atrophy may be related to vascular disturbances or that it may be a transneuronal atrophy consequent on the interruption of descending cortico-thalamic fibres must also be considered. In regard to the first, it may be said that there is no evidence in the sections of any interference with the vascular supply of the thalamus, and the persistence of sharply circumscribed normal elements in the midst of degenerated areas is inconsistent with such an interpretation. As regards the possibility of transneuronal atrophy, we may note that in this type of atrophy, such as may occur in the lateral geniculate body after section of the optic nerve, the cells undergo considerable shrinkage and chromatolytic degeneration, but the cell-bodies do not show the complete disappearance which typically occurs in most neurones of the central nervous system after section of their axonal processes. In any case marked transneuronal atrophy is an unusual phenomenon in the brain and, so far as is known, is limited here to the lateral geniculate body. Experiments by one of us has shown that it does not occur in the sensory nuclei of the thalamus after interruption of ascending sensory tracts, and even in the lateral geniculate body it does not occur to any conspicuous extent in some mammals (e.g. rat and ferret). Lastly, the type of degeneration and accompanying gliosis observed in the present case is precisely similar to the reaction which is seen in different thalamic elements after localized ablation of the cortical areas on to which they are known to project.

It appears, then, that in the human thalamus, the centre median nucleus is the only element which does not project on to the cortex (apart from the few small cells of the subependymal zone). This observation clearly has an important bearing on the question as to how far thalamic activity can proceed independently of the cerebral cortex in man. Unfortunately nothing certain is known regarding the connections of the centre median nucleus. We have noted the possibility that it may project on to the corpus striatum, but we have also pointed out that the case of Le Gros Clark and Ritchie Russell, in which complete degeneration of the centre median nucleus was associated with a very limited lesion of the putamen, does not lend much support to this view. Several authors have described the termination in the centre median nucleus of ascending sensory tracts, particularly fibres of the trigeminal fillet. Here again, the evidence is equivocal, for it can be demonstrated that at least some of these fibres merely pass through the nucleus on their way to rostral levels of the ventral nucleus (Le Gros Clark, 1936). The centre median nucleus has

sometimes been regarded as a phylogenetically ancient element of the thalamus, mainly it seems because of its medial position. Comparative anatomical studies, however, are not in harmony with this conception, for, in the primates at least, the nucleus is much smaller and less clearly defined in lower forms, and becomes progressively better differentiated and relatively larger in an ascending scale of primates leading up to Man. However, the possibility must be entertained that the nucleus, in the circumscribed form in which it is found in higher primates, may represent intralaminar nuclear elements which have been displaced and collected together in one mass as the result of pressure exerted by the growth of the main nuclei of the thalamus in among which they lie in lower mammals.

In conclusion, it may be noted that striatal connections have been ascribed to a number of thalamic nuclei (besides the centre median nucleus) by various authors. The fact that in the present case these nuclei have undergone complete atrophy, while the basal ganglia have not been affected by pathological destruction, is not consonant with this view. In other words, it has yet to be proved that any of the nuclear elements of the thalamus proper are directly connected by efferent fibres with any part of the corpus striatum.

Summary

Clinical and pathological details are given of a case in which a hemiplegia, acquired in childhood, is associated with diffuse atrophy of the corresponding cerebral hemisphere and conspicuous atrophy of the optic thalamus.

With the exception of a few specified areas the cortex is replaced by spongy glial tissue from which almost all the neurones have disappeared. The result is practically equivalent to an experimental hemidecortication.

Thalamic atrophy is practically complete on the affected side with the exception of the centre median nucleus, the lateral geniculate body, and a narrow subependymal zone of small cells. From this it is concluded that all other parts of the thalamus are concerned with the projection of impulses on to some part of the cerebral cortex. The connections of the centre median nucleus remain obscure.

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ACOUSTIC TUMOURS

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IN the literature the paper of List (1932) covering Cushing's material is the single example of a comprehensive statistical survey of the immediate and late results concerning operations for acoustic tumours. Even List's paper, valuable though it is, does not bring sufficient information to enable the reader to form his own opinion concerning the late results, especially earning capacity and morbidity among the survivors. This scarcity of reports indicates, to my mind, that the results are poor, and I am afraid we must confess that the results of surgery in acoustic tumours are not comparable to those obtained in other types of benign tumours. This, of course, has always been so, only the problems have shifted in so far as we now are not so much concerned with the immediate mortality, which has been reduced to reasonable proportions, but with the late results.

Intracapsular Enucleation

In 1933 I reported my experiences with the intracapsular enucleation up to 1st June, 1930. The results are shown in Table 1. In the bottom row of this table are the figures as they appear when this table is brought up to date. The late mortality due to recurrences has now risen to 56 per cent. of those surviving operation, or 41 per cent. of the total number of cases. Among the cases still living there are three cystic tumours which are all completely well. Three or four of the remaining cases are also well ; the rest are invalids. It is obvious that in the case of the cystic tumours and of those with solid tumours which are well after 10 years or more, the tumour has not continued to grow. We can therefore count upon about 10 per cent. of the acoustic tumours being cystic and another 10–20 per cent. to be stationary, a statement that is also born out by some of List's figures. Unfortunately there is no way of knowing at operation whether a solid tumour is growing or not.

TABLE 1.—INTRACAPSULAR ENUCLEATIONS 1923–1930

NO. OF CASES	MORTALITY	DIED LATER OF RECURRENCE	AVERAGE SURVIVAL PERIOD AMONG LATE DEATHS	AVERAGE SURVIVAL PERIOD OF THOSE STILL LIVING
34	9, or 27·7%	12, or 48%	3 years	5 years
34	9, or 27·7%	14, or 56%	3 3/4 years	10 years

* Read at the Third Neurological Congress, Copenhagen, 1939.

Except in the case of stationary tumours the results obtained with the intracapsular operation were extremely poor. All the other cases died from recurrence, usually within 4 years. Their period of relief was also comparatively short, signs of recurrence usually appearing within two or three years, and hardly any of these cases was really well and fully capable of work for any considerable time.

From List's paper we know that Cushing gradually brought down the immediate mortality in the intracapsular operation to a very low figure. However, the late results do not appear to be much different from those obtained in the above series. Thus, of the survivors of the operation who could be traced, 27·2 per cent. died from recurrence after an average survival period of nearly 5 years. That this figure is no greater probably depends upon the relatively very large number of patients who were operated on during the last three or four years and therefore would not begin to figure in the recurrence mortality statistics until some years later. It would be of great interest if the statistics of List were brought up to date.

With regard to morbidity among the survivors 31 per cent. of the traceable survivors were complete invalids, another 31 per cent. practically complete invalids, but they were able to help themselves and had no subjective complaints. Thirty-eight per cent. were partially or completely able to work.

It does not seem unreasonable to expect that if List's statistics were carried up to date they would indicate that perhaps 20–30 per cent. of the total number of cases harbour inactive lesions, which do very well provided the intracapsular operation has been sufficiently complete to release the cerebrospinal fluid pathways, but that the remaining cases are dead from recurrence, being more or less incapacitated during their survival period.

Radical Operation

Before turning our attention to my material from 1930 onwards it is necessary to say a few words concerning the terminology to be used. By radical or complete removal is understood that all macroscopically visible tumour tissue has been removed. A subtotal removal is one where complete removal has been attempted but found to be impossible, usually because of technical difficulties which made the danger of causing irreparable damage to the brain stem too great. An intracapsular enucleation, finally, is an operation which is deliberately incomplete. As executed during the last 10–12 years it coincides fairly well with what List has called radical intracapsular enucleation in his statistics.*

A general survey of the results with regard to immediate and remote mortality is shown in Table 2. The mortality is lowest in the group of radical operations. This seems surprising ; the reason is that into this group fall the majority of favourable cases ; moreover the control of haemorrhage is more reliable when no trace of tumour is left behind. The subtotal removals are a less favourable group ; they consist of cases where the technical difficulties

* My assistant, Dr. Aage Nielsen, has collected and followed up the entire material. His study will be published in the near future.

were greater than in the preceding group, though the most dangerous step in the radical removal of an acoustic tumour, the dissecting of the internal stalk of the tumour from the pons, was omitted. The fact that it has been attempted, however, in the majority of these cases probably accounts for the comparatively high mortality.

TABLE 2.—ACOUSTIC TUMOURS, 1930–1939

	NO. OF CASES	NO. OF OPERATIONS	OPERATIVE MORTALITY	CASE MORTAL.	DIED LATER
Complete extirpations ..	75	75	14, or 18·7%	18·7%	4, or 6·6%
Subtotal extirpations ..	27	28	6, or 21·4%	22·2%	1, or 5%
Intracaps. enucleations ..	28	29	8, or 27·6%	28·6%	4, or 20%
Total	130	132	28, or 20·7%	21·5%	9, or 8·8%

The intracapsular group is even less favourable in view of the operative results. The indications have been somewhat variable during the period covered by this statistical review—old age, poor general condition, a very advanced tumour stage being some of the principal reasons for not attempting a radical operation. In a number of cases the urgent necessity to save the facial nerve has been the deciding factor ; these cases might of course otherwise have been quite favourable for complete removal. The relatively high mortality also depends to a considerable extent upon the fact that a number belong to the early cases in the series.

The remote mortality in groups II and III was, in every case, due to recurrence of the tumour. In group I three cases died from old age, carcinoma of the stomach and septic infection, respectively, several years after the operation. In the fourth case a tumour " rest " the size of a pea was found attached to the pons at autopsy. Whether this tumour was the cause of death is uncertain.

Increasing experience has made it possible gradually to lower the mortality following radical removal of the tumour as is seen in Table 3.

TABLE 3

YEAR	NO. OF CASES	CASE MORTALITY, PER CENT.	DIED LATER	FULL EARNING CAPACITY, PER CENT.	EARNING CAPACITY DIMINISHED, PER CENT.	UNABLE TO WORK, PER CENT.
1931–33	19	26·3	1 (old age)	7·7	69·2	23·1
1933–35	19	21·1	1 (recurrence ?)	14·3	50	35·7
1935–37	19	21·1	2 (sepsis, carcinoma stomach)	21·4	50	28·6
1937–39	18	11·1	0	6·3	81·3	12·4

Turning our attention now to the post-operative morbidity as measured in terms of capacity for work, we find that comparatively few of the survivors ever attain full earning capacity. The intracapsular groups make a comparatively good showing because some of the bad cases have already died from

recurrence. In the course of time only those cases having stationary tumours remain, and these will for the most part, when they have not become blind before operation, fall into the group of full earning capacity.

Among the radical and subtotal groups the majority have some defect which limits their capacity for work. These defects are of various kind and are sometimes difficult to define exactly, the most common being poor vision, cerebellar disturbances, general weakness. That cerebellar disturbances are less important than one might imagine is shown by the fact that the majority of survivors have normal gait and station (Table 4). It should also be taken into account that following a complete removal the time for convalescence and then for re-education is a long one, often a year or even two, and a number of the radicals who still use a stick are recent cases where the process of re-education has not yet been completed. Also this group is burdened by a number of early cases when the technique was still comparatively crude and where for this reason severe cerebellar disturbances and in two cases a more or less complete Wallenberg syndrome followed.

TABLE 4

	NO. OF CASES	CASE MORTALITY PER CENT.	DIED LATER PER CENT.	FULL EARNING CAPACITY PER CENT.	EARNING CAPACITY DIMINISHED PER CENT.	UNABLE TO WORK PER CENT.	WALKS NORMALLY PER CENT.	WALKS WITH STICK PER CENT.	UNABLE TO WALK PER CENT.	BLIND PER CENT.	CLINICAL SIGNS OF RECURRENCE PER CENT.
Complete extirpations..	75	18·7	6·6	14·3	66·1	19·6	54·4	42·1	3·5	5	0
Subtotal extirpations..	27	22·2	5	15	70	15	65	30	5	5	10
Intracaps. enucleations	28	28·6	20	37·5	37·5	25	50	37·5	12·5	10	15

That the rate of morbidity has been considerably improved upon is shown in Table 3. In the last group of cases only 12·4 per cent. were completely unable to work, and these mainly on account of poor vision which had been present before operation. It is also certain that a large number of cases belonging to this last group who, at present, have a diminished capacity for work will in the course of time, when their re-education is completed, regain their full capacity for work.

I think it is fair to conclude that the intracapsular enucleation gives excellent results in those cases where the tumour is stationary or grows at an exceedingly slow rate. Unfortunately we cannot, except in the case of the cystic tumours, determine beforehand or at the time of operation the future behaviour of the growth. In the majority of cases, probably around 70 per cent., we have to face the presence of an actively growing tumour, and in these cases the only way to restore any considerable number of patients to health and social usefulness is to remove the tumour completely.

Post-operative Facial Palsy

At this stage it is necessary to consider the facial nerve. Of all defects following radical removal of an acoustic tumour this is the most common and the most obvious. The facial disfigurement, which can at best be very incompletely improved by the various plastic and anastomosing operations, is always a very unpleasant sequel to an otherwise successful operation and may have very grave consequences for the individual, particularly in the case of young girls.

Isolated reports of saving of the facial nerve in operations entailing complete removal of acoustic tumours have appeared in the literature, but I have been unable to find any reports on continued efforts in this direction or any statistics bearing on this problem. In my material the facial nerve has been saved occasionally more or less by chance in the earlier years of the radical operation. However, it was not until the dangers and difficulties of the radical operation had been to some extent overcome that systematic efforts to save the facial nerve were made, even when the tumour was completely removed. Since January 1937 an attempt in this direction has been made in every case. The number of complete extirpations done since January 1937–June 1939 was 23. The facial nerve was saved anatomically in 15, or 65 per cent. of the cases. In all these cases except one, the nerve was so much traumatized during the operation that the homolateral side of the face was paralysed immediately following operation. In some of these cases a partial reaction of degeneration was observed some weeks after operation, and in the majority the reaction of degeneration was complete. In either case regeneration of the nerve took place within some months or a year (Fig. 1), though occasionally facial function failed to return.

Fig. 1.—Case 7, 1937. Right sided acoustic tumour completely removed 1st January, 1937. Pictures taken May 1939.

I have no doubt that these results can be improved upon and that the facial nerve can be saved in most cases where a complete removal is technically possible. The most important requisite in this respect is, as every neurosurgeon knows, that the " capsule " of the tumour should have a certain toughness.

My conclusions with regard to the policy to be pursued in acoustic tumours can be formulated in the following way. In cystic tumours nothing need be done except the removal of tags of tumour tissue from the cyst wall and cauterizing the latter with some fixative. In all other cases the complete removal of the tumour should be done if possible. However, if, after the lower pole has been mobilized it appears probable that the tumour, for technical or other reasons, cannot be completely removed or if the conservation of the facial nerve is of special urgency, care should be taken that the facial nerve is not injured during the remaining procedure, which terminates as a subtotal removal. In these cases a tiny bridge of tumour tissue is left covering the facial nerve and the side of the pons in the region of the emergence of the VIIIth and VIIth nerves, while the rest of the tumour is removed. For technical and other details I must refer to Dr. Nielsen's paper.

Summary

The mortality in radical operations in 75 cases of acoustic tumour, which is 18·7 per cent. in the whole series, has been brought down from 26·3 per cent. in the years 1931–33 to 11·1 per cent. in the years 1927–1939. During the last 2 years the facial nerve has been saved in 65 per cent. of the cases where the tumour was completely removed.

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A CRITICAL REVIEW

THE PATHOLOGY OF CEREBRAL GLIOMAS

BY

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A CRITICAL review of the historical development and the present state of the pathology of cerebral gliomas is justified for different reasons. The first is the frequency of the condition : over 1 per cent. of all deaths are due to intracranial tumours (Ewing, 1928 ; Weil, 1934 ; Cox, 1935 ; Greenfield, 1936 ; Courville, 1937 ; Flock, 1937), about half of which are gliomas (Tooth, 1912, and all following authors). According to Peers (1936), intracranial tumours form 16·8 per cent. of all malignant neoplasms in man. Secondly, the number of papers written on this question during the last 50 years and the frequent contradictory opinions, make it almost impossible to reach a clear conception without an intimate acquaintance and an extensive personal experience of the subject. Thirdly, the whole glioma literature of the last 15 years practically ignores the previous work to such an extent that many previously well-established facts have completely been forgotten or often rediscovered in good faith by authors who believe that there was no worth-while glioma research before Bailey and Cushing (1926). Fourthly, the evolution of investigations on gliomas is extremely instructive from a general point of view : it demonstrates clearly that the study of a natural phenomenon transforms itself into sterile discussions as soon as the methods and principles generally applied in natural sciences are replaced by predominantly scholastic methods more devoted to the establishment of names, classifications, statistics, and theories than of facts. Finally, some recent developments of glioma research justify the hope that in the near future it will emerge from the deadlock of interpretations in which it has struggled for about 20 years and will become again a fruitful branch of natural sciences.

To contribute to this evolution is one of the essential purposes of this paper. This purpose determines both the form and content of the review. Owing to the limited space, it is impossible for the review to be complete. It has to deal essentially with the historical evolution of our knowledge of facts, but not with the creation of new names and systems for things known before under other names. This philological aspect of the question will be considered only in so far as it is necessary to understand the evolution of the glioma problem. Strong

criticism has the object of impeding continuous waste of time and material by researches the uselessness of which is evident. Especial weight shall be given to the author's researches carried out during the last 8 years on 130 gliomas obtained at necropsy. These were studied by a new method allowing a particularly complete examination of the tumours.

The Classical period of Glioma Research

Gliomas with their macroscopical resemblance to normal brain tissue (Burns, 1800) were known long before Virchow ; by the English under the name of " medullary sarcoma " (Abernethy, 1804), as " encéphaloïde " by the French, and by German authors as " fungus medullare." This was the period of macroscopical research. Virchow (1863/1865) not only created the name " glioma " but—what is much more important—he opened the period of combined macroscopic and microscopic study of these neoplasms. He distinguished two main groups of brain tumours, glioma and sarcoma, the latter term having for him not a histogenetic but a purely descriptive sense. He characterized gliomas as follows : these are often enormous tumours of brain-like appearance with very slow clinical evolution ; never showing a clear limitation towards the normal brain tissue, but resembling more a hypertrophy of the involved parts (the general architecture of which seems preserved) than real neoplasms. Microscopically they are formed by a proliferation of glia cells and sometimes of glia fibres : in the latter case, the tumour is rather hard ; in the former soft. Owing to extensive vessel proliferations or " myxomalike " degeneration in these tumours, he still distinguished " teleangiectatic " and " myxogliomas." Although his histological study was handicapped by the immaturity of the histology of that day, his general description very clearly characterizes the tumour known to-day under the name of " cerebral astrocytoma " ; he even emphasized the occasional coexistence of quite variable histological structures in one and the same tumour. His cerebral sarcomas have the following characteristics : as opposed to the gliomas, they frequently have a spherical shape and definite boundaries, but they sometimes show also a more imperceptible transition towards the surrounding tissue. Extensive hæmorrhages often provoke an " apoplectic " clinical evolution. Microscopically they are distinguished from the gliomas by their high cellularity and much larger, often fusiform, shape of cell, by their high vascularity and pronounced fatty degeneration. There is no doubt that these tumours correspond to what is now called " glioblastoma." Thus, the clinical and pathological differences between the two main groups of brain tumours which dominate all modern glioma classifications had been perfectly characterized in 1865. Recent systematic researches (Scherer, 1940 *a*, *b*) have entirely confirmed Virchow's description of the general pathology of these groups, while the modern, essentially cytological systems have replaced many previously clear notions by considerable confusion.

The methods and findings of Virchow are still of the greatest importance. The method is that of the objectively described, combined macro- and micro-

scopical study, giving in principle the same weight to the macroscopical aspect —forms of growth and extension, general architecture, structural variations from one place to the other, degenerative lesions, and clinical course—as to merely cytological investigations. He determined the methods of glioma research for about 50 years. The undoubted poverty of Virchow's histological descriptions and the tremendous progress realized by histology during this period explain why the histological point of view has become more and more predominant since the beginning of this century. Unfortunately, the slowly increasing custom of neglecting other aspects of gliomas in favour of cytological studies is accompanied by the tendency to violate or neglect facts in favour of preconceived ideas or systems based on the study of isolated aspects of glioma pathology. Let us follow now the steps of this evolution of methods, knowledge, and ideas.

Stroebe's (1895) work furnishes the first really detailed microscopical description of gliomas, and this fact certainly has more importance than the theoretical discussions and errors of interpretation found in his paper. He confirmed the essential differences of macroscopical behaviour and mode of growth between " glioma " and " sarcoma " as described by Virchow. He was the first to use new " specific " methods for the staining of the different histological structures. But—in contrast to most modern investigators, hypnotized by such methods—he did not neglect a careful study of all other aspects of his cases. He never limited his histological study to an arbitrarily chosen fragment of glioma tissue, but always examined very large parts of the tumours by means either of large celloidin or of numerous small paraffin sections whose exact location in the tumour was indicated. Thus, he discovered that pre-existent nerve cells and fibres are conserved in the midst of glioma tissue, though not in " sarcomas " ; that the leptomeninges are invaded by " sarcomas," but not by gliomas ; the existence of circumscribed " sarcoma " nodules in otherwise typical gliomas ; the frequent small cystic degeneration in " gliomas " ; the existence of numerous glial fibres in " gliomas," their absence in " sarcomas " ; the absence of mitoses and highly polymorphous cells in the former, their frequency in the latter ; the essentially infiltrative growth type of " gliomas," using the pre-existent fasciculation of nerve fibres, which modifies the otherwise round shape of the tumour cells to an elongated one. This important notion that the cell form in gliomas may depend upon mechanical influences exercised by the pre-existent brain tissue has been entirely forgotten by most modern writers, who implicitly consider the forms of glioma cells as an exclusively intrinsic factor of " histogenetic " significance.

Henneberg (1897) and Storch (1899) confirmed Stroebe's description in all essential points, except for the differential significance of glial fibres. While Stroebe excluded the diagnosis of a " glioma " in the absence of glial fibres and " spider-cells " (= fibrillary astrocytes), Storch emphasized that gliomas have the same property as all other tumours to become so atypical that no more typical structures (e.g. fibres) are formed. In such cases he considered the entirely diffuse, unlimited growth type as sufficiently specific to justify in itself the diagnosis of a " glioma." Here we see the implicit transition of the purely

descriptive sense of these names into a definite " histogenetic " sense : for Virchow, sarcoma in the brain and elsewhere meant nothing but a tumour of a given macroscopic and cellular *aspect* ; since the end of last century, it has meant tumour of mesenchymal *origin*. Glioma research began to leave the field of facts and entered that of deduction. Most papers of the following 10 years tried to fix the histogenetic position of the brain tumours previously called " sarcomas," and to prove their glial character in spite of the absence of glial fibres. These tumours became known as " gliosarcoma " (Borst, 1902) or " glioma sarcomatodes " (Stumpf, 1911), terms which do not suggest a combination of glial and mesenchymal tumours, but a tumour of purely glial " histogenesis " whose morphology resembles a sarcoma. All further discussions deal with the recognition by morphological methods of the glial histogenesis of a tumour, whose cells do not resemble glia but a (mesenchymal) sarcoma (Ranke, 1911). For a long time (Stumpf, 1911) the growth by diffuse infiltration superimposed on the persisting and pre-existing structures remains the essential criterion for glial tumours of typical or atypical (" sarcomatous ") cellular aspect.

In 1899 Storch clearly described for the first time a brain tumour whose general morphology differed from both the main groups known until then. In a child of 6 years he found a partially cystic tumour of the parietal lobe characterized by a curious papillary perivascular structure, its cells forming " crowns of rays " around the vessels, and in other places tubular structures with a lumen, resembling the central canal of the nervous system. There is no doubt that this is the first description of what is to-day called an " ependymoma." Storch even desribed 3–4 dark corpuscles in the cytoplasm of the tumour cells, which in all probability correspond to the " blepharoplasts " considered as so important for the diagnosis by Mallory (1902) and Bailey (1924). Saxer (1902), Mallory (1902), and Muthmann and Sauerbeck (1903), in masterpieces of careful, methodical, and objective descriptions, created the complete picture of this tumour group. In 1903 the following was known about these tumours : they are distinguished from the other primary brain tumours by an exclusively expansive growth ; they are lobulated and papillary tumours, comparable to intracanalicular fibro-adenomas of the breast (Muthmann and Sauerbeck) ; three structures are encountered : the perivascular " crowns," the cavities lined by ependymal cells, and more cellular parts. Necrosis and calcification of vessels (Saxer) may be present. These tumours are frequently located in the ventricular cavity, especially in the IVth ventricle, but occur also outside the ventricles, in the brain hemispheres (Storch, 1899 ; Saxer, 1902, case I, confirmed later by Fincher and Coon, 1929, and Zülch, 1937), the spinal cord (Saxer, 1902 ; Kernohan, 1932) and the cauda equina (Saxer, 1902 ; Kernohan, 1932). Their ependymal origin is demonstrated for Saxer principally by the cells surrounding the cavities, for Mallory by the blepharoplasts seen in these cells. Saxer already emphasizes the intimate architectural and histogenetic relationship of intraventricular ependymomas with papillomas of choroid plexus, which has been rediscovered more recently.

Thus, at the beginning of this century three main groups of " gliomatous "

tumours were clearly distinguished : (1) one group characterized by purely expansive growth, lobulated and papillary architecture, arrangement of the ependymalike cells around vessels or cavities, situated in the IVth ventricle or in the brain hemispheres, spinal cord, or cauda equina ; (2) one group of slow clinical course, characterized by a diffuse, unlimited type of growth superimposed on pre-existent tissues and formed by " spider cells " (astrocytes) with glial fibres ; tumours of this type have been seen especially in brain hemispheres and brain stem (pons) ; (3) one group of macroscopically well-defined neoplasms, somewhat more circumscribed, formed by immature, sarcomalike cells, but connected to group 2 by a similar infiltrative type of growth, and destroying the invaded tissue more rapidly. Nodules of type 3 may occur in cases of type 2, and transitions between both types are encountered.

During the following 20 years the papers are not very numerous, and become already somewhat more interested in the interpretation than in the establishment of facts. Beside the above-mentioned questions of terminology and histogenesis—which only take a small place in the old literature—two main problems are discussed : that of the mode of formation and growth of gliomas and that of their eventual causal relationship with local malformations (heterotopias). Both are problems of general tumour research applied to gliomas. The first problem is, whether gliomas grow *aus sich heraus* by simple progressive division and migration of the cells which primarily constitute the tumour (Stumpf, 1911; Ranke, 1911; and most other authors) or by progressive transformation of the primarily normal glia surrounding the glioma (Storch, 1899) or whether they constitute primarily diffuse neoplastic glia proliferations (Rindfleisch, 1886 ; Henneberg, 1897 ; Landau, 1910). No clear solution to this question could be reached, except for the rôle played in the formation of gliomas by eventual local disturbances of the brain's evolution during the embryonal period. On the whole, these theoretical considerations never dominate the descriptions. Thus, in 1912, an excellent descriptive and highly comprehensive study was given by Tooth. This is the first glioma study which tries to link the clinical course and the morphological structure of the cases, all previous papers having either neglected the clinical aspects, or described them carefully only in isolated cases (Henneberg, 1897). For the first time Tooth used extensive neurosurgical experiences for the study of gliomas, and drew therapeutical conclusions. Further, it is the first study based on a very large material ; this is especially important : (1) because all previous works concern small numbers of cases ; (2) because most subsequent papers, although using even larger series of cases, never give such detailed and objective description as is found in Tooth's paper. Tooth created neither new names nor schemes, and that obviously is the reason why his paper is practically forgotten by all following authors. He first made the important statistical statement that gliomas are by far the most frequent intracranial tumours, forming 127 out of his 258 verified cases (49·2 per cent.). He insisted again upon the slow clinical course of the tumour type known to-day as cerebral " astrocytoma." His case 2 is a typical cerebellar astrocytoma, and he removed it successfully without recurrence. He describes the frequent occurrence of multiple small cysts and rarely of a single

large cavity in the " benign " ; the almost constant presence of extensive necrosis in the " malignant " type of gliomas ; and insisted upon the clinical importance of these degenerative lesions. He was the first to emphasize the importance of curious vascular proliferations in the more malignant, highly cellular types of gliomas and compared them to " glomerular " formations. He emphasized not only the occurrence of quite different histological tumour types in different places of one and the same glioma (a fact already known to Virchow, Stroebe, and Henneberg), but gave to this co-existence a dynamic interpretation : " benign " glioma types may develop into malignant ones. He even supposed " with the greatest possible diffidence " that incomplete extirpation may favour such a malignant transformation because he observed a change of the tissue character in the sense of progressive malignancy by means of subsequent operations. On the whole he considered gliomas, with some exceptions, as inoperable tumours, although incomplete removal is justified by the periods of relief obtained this way.

Tooth's work is one of the most comprehensive papers ever written on gliomas, especially because of his vivid appreciation of the dynamic character of these neoplasms and the very critical use he made of operation specimens.

The Histogenetic Period

In 1918 Ribbert, whose influence was already responsible for the progressive infiltration of more speculative histogenetic and ætiological discussions into the glioma literature since the beginning of this century, published his paper " On the Spongioblastoma and the Glioma." This paper would not be worth mentioning were it not for the disastrous influence it exercised both on the methods and the ideas dominating the glioma research during the following 20 years. Until then authors considered histogenetic and other theoretical discussions as accessory to the facts described ; Ribbert and his followers group arbitrarily chosen facts around hypothetical systems. His paper gives a rather poor description of schematical drawings of arbitrarily chosen areas, whose position in the tumour he does not indicate (growth zone ? central parts ?). The drawings are of different but otherwise undescribed tumours, and show " epithelial " formations which, in his opinion, proved the origin of gliomas from slumbering embryonal mother cells. The conclusions of his work—obtained by merely theoretical deductions—can be summarized as follows : differentiated glia cells can never return to a lower degree of differentiation. Thus, gliomas, glioblastomas, spongioblastomas must be explained by the persistence of embryonal cell elements arrested at different stages of their differentiation. Probably the topography of the " dysontogenetic " disturbance also plays a rôle in the structure formation of the resulting gliomas. The objective reader finds absolutely no facts in this paper that would justify these conclusions. All that can be concluded from Ribbert's illustrations is that some of them probably come from ependymal tumours.

Ribbert's paper opens the period of glioma research characterized by the arbitrary emphasis laid on merely cytological studies, neglecting almost com-

pletely the numerous other aspects of glioma pathology. The dominating method becomes now the cytological study of a fragment of glioma tissue studied with the implicit supposition that it is in any case representative for the whole tumour, the possibility of cellular and structural variations in different parts of the tumour not being seriously considered. Differences between gliomas which are not of cytological or " histogenetic " nature are inadequately studied and have, in any case, to be subordinated to these sole determining characteristics. This tendency has been strengthened by the contemporary extension of the use of so-called " specific " methods of impregnation for the different subdivisions of glia cells isolated by the Spanish school.

The French school alone resists these histogenetic interpretations. Roussy, Lhermitte, and Cornill gave, in 1924, a very clear histological description which distinguishes (fibrillary) astrocytomas, four subgroups of afibrillar gliomas (round cell, fusiform, polymorphous, and ameboid types), glioblastomas and spongioblastomas, and puts the ependymomas and choroid plexus tumours together in one group separated from the other gliomas. The illustrations of Roussy and Oberling's " Atlas " (1931) are among the best which have been published on the histology of gliomas, especially for didactic and diagnostic purposes. Their description obviously adds no essentially new facts to what was known before, and even constitutes a regression in so far as it considers too exclusively the histological pictures detached from all other characteristics. It is, however, important for two historical reasons : (1) as far as histology is concerned, the authors do not violate the facts in favour of schemes ; (2) they maintain this objective description of facts and reject explicitly (Roussy, 1928 ; Roussy and Oberling, 1931) the histogenetic schemes at a time when the investigators of the whole world were defending them as a sacred dogma.

This attitude, prepared by Ribbert (1918) and Globus and Straus (1925), finds its most dogmatic expression in Bailey and Cushing's work *A Classification of the Tumors of the Glioma Group on Histogenetic Basis with Correlated Study of Prognosis* (1926) ; its title indicates clearly its tendency. Their work first gives a schematic description * of the histogenesis of the brain and the cell forms encountered in it, followed by a chapter describing the corresponding " histogenetic cellular types " seen in gliomatous tumours. The following chapter contains the classification of gliomas according to the histogenetic cellular types encountered in them. Although the authors admit that a glioma is rarely composed of a single type of cells, they affirm that a classification according to the " predominant " type of cell (Bailey and Bucy, 1930) is possible in most instances. As no exact method of determining the predominant cell in an objective manner is indicated, it seems to correspond to a simple impression. A last chapter dealing with the clinical correlations confirms the old rule that tumours composed of less differentiated cells are more actively growing than those composed of more highly differentiated cells ; that almost half of all classified gliomas belong to the latter group and thus, except for an eventual inaccessible position, may be regarded as comparatively benign lesions.

* Bailey's scheme of the normal histogenesis of the brain is far from being generally recognized. Hortega (1932) defends a quite different conception.

This study was based on 412 verified gliomas, including 167 necropsy specimens. The different histological differential stains used are carefully indicated, but there is no indication allowing a judgment whether the necropsy material has been more completely examined than it is possible for biopsy fragments. Large celloidin sections throughout the whole tumour are mentioned for " several " cases of " spongioblastoma multiforme." In any case, local variations, behaviour of growth zones, and pre-existent tissues are not taken seriously into consideration and the important link between the merely cytological descriptions and the macroscopic appearances is lacking.

Only 254 of these 412 cases could be classified in the following scheme :

	NUMBER OF CASES.	AVERAGE DURATION IN MONTHS.
Medulloepithelioma	2	8
Neuroepithelioma	0	—
Medulloblastoma	29	17
Pinealoblastoma	3	12
Pinealoma	5	19
Ependymoblastoma	5	10
Ependymoma	7	32+
Spongioblastoma :		
(*a*) multiforme	77	12
(*b*) unipolare	9	46+
Neuroblastoma	2	25
Astroblastoma	13	28+
Astrocytoma :		
(*a*) protoplasmaticum	52	67+
(*b*) fibrillare	39	86+
Oligodendroglioma	9	66+
Ganglioneuroma	0	—
(Double tumours : 2)		

Presented in this way, the classification seems extremely clear and attractive both for didactic purposes and for the surgeon who hopes to obtain from the pathologist exact indications for therapy and prognosis. The pathologist, however, would be *a priori* sceptical in the presence of such a scheme. He knows too well that the histogenesis of immature tumour cells is always hypothetical ; he knows too that identical histogenesis does not mean identical biological behaviour. To test the real value of this classification let us see now whether the scheme corresponds to facts. To test the value of the methods employed, let us see what are their final results, their influence on contemporary glioma research, and the new facts they really brought forward. Bailey and Cushing's monograph can be appreciated only when considered together with their other publications.

Two groups of the scheme are not represented by any cases.* On the other hand, a high percentage of cases remained unclassified. It is true that this seemed due in many cases to an insufficient amount of tissue being examined ; however, in 1933 Bailey still quotes the high number of 67 " unclassifiable and rare types " aside of 378 classified cases. Furthermore, Bailey and Cushing's as well as Globus and Strauss's (1925) previous description of the

* Horrax and Bailey (1925), Globus and Silbert (1931) and others describe pinealomas as histologically well-characterized tumours whose structure seems to repeat the embryonol structure of the pineal gland. The tendency to classify almost all pineal tumours (except teratomas) in this group, once again, does not take the facts into account. Pathologists know that tumours of quite different structures occur in the pineal gland (Berblinger, 1926). One of the cases published by Baggenstoss and Love (1939) resembles closely an ependymoma. On the other hand, one begins to call " pinealomas " certain rare diffuse ependymal tumours of the IIIrd ventricle and its neighbourhood (Ford and Muncie, 1938) in spite of a normal pineal body and only because of apparent histologic resemblances (Mackay, 1939).

" spongioblastoma multiforme " (a new name for the tumours called previously gliosarcomas) make it obvious that the different tumours united under this name are by no means characterized according to their histogenesis, most of their cells being atypical to such a degree that they have not the slightest resemblance with any mature or immature glia cell of the brain. This has clearly been recognized by Penfield (1931). If the spongioblastoma group corresponds to the old gliosarcoma, the astrocytoma is the classical " glioma " and the ependymoma and ependymoblastoma correspond to the papillary tumours well known since the beginning of this century. No essential new facts have been added, neither clinically nor anatomically, to what was previously known about these groups which form the big majority of all gliomas. Their exclusively histological definition has consigned to oblivion for long years, many of their other morphologic characteristics previously established and which are at least as important as their cytology (Scherer, 1940, *a* and *b*).

What new facts have been discovered ? It has been said by Bailey (1932, *a*) himself and others that the sole really new fact was the discovery of oligodendrogliomas, and that otherwise the main importance of Bailey and Cushing's monograph was to have stimulated research and interest in gliomas (Greenfield, 1936). Both statements are not entirely justified. Beside oligodendrogliomas Bailey and Cushing have brought to our knowledge two highly important glioma groups not clearly isolated before them. Undoubtedly they stimulated to an extreme degree the interest in glioma research, but unfortunately in a wrong direction. The unfavourable influence their histogenetic doctrine exercised upon research is most clearly visible in Bailey and Cushing's work itself, as may be demonstrated by some examples.

In 1925 these authors published their important work on cerebellar medulloblastomas. Although isolated instances of probably identical tumours had been described a long time before them as sarcomas or neuroblastomas, Bailey and Cushing have the great merit of having made a real morbid entity of this group. This important result was not obtained by the merely cytological study which lead to the conception that these tumours are formed by " medulloblasts " (histogenesis considered as highly hypothetical by Penfield, 1931 ; Cox, 1933 ; Russell, 1939 ; and others) but by a careful objective study of life history, macroscopic appearance, point of origin, growth type and spread, and, finally, architecture and cytology. The result is the following : in children (rarely in adults) there frequently occurs a rapidly growing, soft, reddish-grey, rather well-defined tumour, originating from the roof of the IVth ventricle, filling and dilating its cavity and invading moderately the overlying cerebellar tissue, having sometimes a pronounced tendency for extensive spread throughout the meningeal and subarachnoid space of spinal cord and rarely of brain. These tumours are extremely cellular, their cells generally forming a structureless mass, but sometimes also " rosette-like " formations. The rapidly growing, undifferentiated cells have a very scanty cytoplasm, are round, sometimes contain elongated nuclei containing a dense net of chromatin, and resemble those of a round cell sarcoma. Mitoses are very frequent. A mesenchymal stroma is well developed. Thus a tumour entity is described in a way which permits

easy recognition, and at the same time the biological and clinical behaviour of these tumours has become understandable. If the authors had continued to study their whole glioma material in this way, the science of gliomas would probably offer to-day a quite clear aspect instead of the disappointing confusion now existing. But Bailey was fascinated by the histogenetic doctrine to such a degree that one year later a whole monograph is based on the fiction that merely cytological or " histogenetic " tumour entities (1) exist and (2) are in themselves morbid entities : the cytology alone determined the place of a glioma in the classification, and this view was justified by the clinical correlation, a different average duration of the life-history corresponding to every one of the histogenetic groups. The result was the creation of cerebral medulloblastomas, of fibrillar and afibrillar astrocytomas without clear-cut distinction of their cerebral or cerebellar location, etc.

Cushing, who had stimulated the elaboration of the classification for *clinical* purposes, obviously became rapidly aware (1931, 1932, 1937) that many facts were in contradiction with the doctrinal classification. Thus he created (1931) the group of cerebellar astrocytomas because their pathological and clinical behaviour proved to be absolutely different from the cerebral astrocytomas in spite of an apparently identical histogenesis. The isolation of this new morbid entity (frequently cystic, rather circumscribed, slowly growing, predominantly astrocytic tumours occurring in the vermis or cerebellar hemispheres of children and offering a good opportunity for extirpation without recurrency) is again a result of great and undiscussed * importance. It was again obtained not by the application of the cytological and histogenetic principles, but in spite of them. As a contrast, its subsequent application lead to the unfortunate creation of the group of cerebral medulloblastomas. Regarding this group, Cushing stated later on (1932, 1937) that they behave much more like oligodendrogliomas and Bailey (1938) recently admitted that he has become sceptical about these cerebral medulloblastomas, which probably were mistaken oligodendrogliomas. The neuroepithelioma, another doctrinal creation, has been recognized in the meantime as identical with the ependymoma (Kernohan, 1932; Bailey, 1938; Russell, 1939). The existence of a cerebral medulloepithelioma is not less hypothetical (see Russell, 1939). The oligodendrogliomas finally, the real histogenesis of which had been proved by means of successful specific impregnations by Bailey and Bucy (1929), Kwan and Alpers (1931), Hortega (1932), Környey (1937), and others, undoubtedly contain tumours of quite different behaviour : slowly and rapidly growing (Penfield, 1931 ; Cushing, 1937) ; well defined (Bailey and Cushing, 1926 ; Russell, 1939) and extremely diffuse (Löwenberg and Waggoner, 1939) ; invading extensively the ventricular system (Greenfield and Robertson, 1933), etc.

From these contradictions, Cushing (1937) concludes logically that a merely histogenetic definition causes entirely erroneous conclusions if it does not take into account the different evolutions of the tumours. As the purpose of the

* Bergstrand (1932*b*, 1937) confirmed the essential facts, but interpretated them as malformations and not as true tumours. This entirely erroneous interpretation has been refuted by Bucy and Gustafson (1939).

new classification was precisely to create histological types making definite prognosis possible, this statement admits courageously the failure of the system. In spite of this, Cushing continued with the tremendous majority of authors to apply this system, with the result that tumours of quite different behaviour remain joined under the same name (cerebral and cerebellar astrocytomas) and vice versa. The fact that many authors felt this obvious incongruity between facts and doctrine is expressed by the innumerable modifications of names, schemes, and classifications which form the predominant object of the glioma literature of the last 15 years. They are summarized and discussed in Henschen's (1934) and Bailey's (1938) scholarly reviews, and one must agree with Bailey (1938) that they certainly have brought no serious progress to knowledge. However, this does not prove that progress is not bitterly needed, but only that the right way has not been recognized. If any further proof were needed, it was furnished by Hortega's great work on gliomas (1932). While Bailey and Cushing and most other " histogenetic " investigators made only an incomplete use of the specific methods of impregnation, they are applied here to the utmost and by the hands of their outstanding master. Hortega's work on gliomas constitutes a masterpiece of cytological tumour research which will not be surpassed for a long time. He joins to his excellent technique an absolutely logical application of the histogenetic principles without transgressing the objective description. The result is a classification of gliomas into iso- and heteromorphous glioblastoma, fibrillar and afibrillar astrocytoma, astroblastoma, oligodendrocytoma, and glioepithelioma. In this application of an exclusively histogenetic classification there is no place for clinical or macroscopic aspects, for differences of localization, etc. : thus the medulloblastoma cerebelli disappears completely and is joined to tumours of similar cytological appearance of the brain, called altogether isomorphous glioblastoma. Hortega's astroblastoma is *exclusively* characterized by the astroblastic character of its cells, but not—as defined by Bailey (1938) recently in obvious contradiction with his own principles—" by cells forming striking palisades around vessels," that is by an *architectural* criterion. Thus Hortega's astroblastoma group, according to Bailey (1938), includes many " glioblastomas of rather low malignancy or protoplasmic astrocytomas with a tendency to anaplastic transformation." On the whole, Hortega's work is perhaps the only one which applies the histogenetic principle in a really puritan manner without any inconsequent concession to clinical, biological, pathological, architectural, or other considerations. For that reason it demonstrates in a more peremptory manner than all other publications the fact that this principle in itself is inapplicable for both the pathological and clinical classification of the gliomas.

The struggle between facts and doctrine created numerous compromises, which greatly disturbed the logical unity of the scheme without a satisfactory result. Some of these compromises have already been mentioned. Others concern especially the " spongioblastoma multiforme." For this most frequent and thus most important type of gliomas Penfield clearly recognized in 1931 that it has to be considered outside of the histogenetic scheme, and that its outstanding histological characteristic is a marked proliferation of blood

vessels. The statement that this name covered tumours of quite different aspect and also different clinical behaviour (Deery, 1933) leads to histological subdivisions such as protoplasmic, microcellular, fusiform and multiform glioblastomas (Bergstrand, 1932, *a* and *c* ; Gagel, 1938). None of these merely histological distinctions was able to transform these subdivisions into clearly characterized tumour entities, any more than three other cytological subdivisions (diffuse, piloid, gemistocytic) suggested for the " cerebral astrocytoma " (Elvidge, Penfield, and Cone, 1935 ; Alpers and Rowe, 1937). For the astroblastoma the cytological criterion has been more and more supplanted by an architectural one—the perivascular arrangement around vessels with hypertropied walls (Bailey and Bucy, 1930 ; Penfield, 1931). In spite of this compromise, clinically and histologically the astroblastoma remained a questionable and never well-characterized entity. With regard to cerebral astrocytomas, Cushing (1931, 1932) recognized that many of his cases classified under this name probably should be classified elsewhere, because they were rapidly growing tumours with numerous mitoses. Bergstrand (1932) and Cooper (1935) stated that in numerous cases the cytological distinction between oligodendrogliomas and astrocytomas becomes impossible. These and other similar statements lead to the creation of " transitional forms " expressed in names such as " astroglioblastoma " (Kino, 1935) and others (Levin, 1939). Bergstrand deserves much credit in having emphasized already in 1932 the great frequency of histological transitions between the different cytological " entities." The term " polar spongioblastoma " obviously changes its significance from one author to the other ; Bergstrand (1932), Cox (1934) and Russell and Bland (1934) identify it with Penfield's " piloid astrocytoma " (fibrillary astrocytoma distinguished by elongated cell forms and polar arrangement of its fibres instead of intertwining network) ; Hortega (1932) and Roussy and Oberling (1931) seem to identify it with certain oligodendrogliomas. The tendency to call more and more gliomas in the brain stem " polar spongioblastoma " (see Echols, 1938, and others) is probably explained by the fact that tumour cells of quite different character adapt their shape to the direction of the pre-existing nerve fibres, the " polar " arrangement of which is more pronounced in the brain stem than elsewhere. The very incomplete description of most of the published cases allows no judgment about their real character. Authors with still more imagination consider the elongated form of cells as sufficient to justify the description of a " central diffuse Schwannosis " (Foerster and Gagel, 1934 ; Santha, 1936).

More clinical points of view together with the unsatisfactory results of merely histological researches provoked a considerable number of papers which analysed tumours of a determined localization, such as gliomas of the pons (Buckley, 1930 ; Alpers and Yaskin, 1939 ; and others), of the thalamus (Smyth and Stern, 1938), mesencephalic gliomas (Alpers and Watts, 1935), etc. These papers either deal with tumours of different histological structure in a given localization or bear histological names such as " astrocytomas of oblongata, pons, and midbrain " (Foerster and Gagel, 1939, and others). In the first case, authors often try to force tumours into a given localization : thus Buckley

mentions that in many of his pontine gliomas the cerebellum was much more involved than the pons ! In the latter case the tendency is again to force tumours into the histological diagnosis given in the title. Case 6 of Foerster and Gagel's astrocytomas is obviously a glioblastoma. These examples show that the tendency, characteristic of the whole histogenetic period, to schematize facts, has unfavourably influenced these otherwise very worthwhile papers. Therefore the conclusions and the statistics based on them have to be accepted with the greatest reserve. It is significant that Smyth and Stern (1938), who examined their cases very completely, renounced immediately schematic histogenetic diagnoses of most of the described cases. Even the use of the method of tissue culture has been subordinated to the histogenetic ideology (Kredel, 1928 ; Buckley, 1929 ; Buckley and Eisenhardt, 1929 ; Russell and Bland, 1933, 1934 ; and Cox, 1937). It generally leads to the somewhat sterile conclusion that the cells grown in the cultures resembled those seen in the microscopic sections of the glioma from which the cultures were taken. Only Russell and Bland (1934) made an important statement : cells from a histologically typical " polar spongioblastoma " formed typical astrocytes in the cultures. They draw the conclusion that Bailey's polar spongioblastoma is in reality a piloid astrocytoma (Penfield).

Schwartz (1932, 1936) and later Ostertag (1934, 1936) tried to replace the histogenetic classifications by the elaboration of localization types of gliomas, in the same manner as the localization types of meningiomas elaborated by Cushing. The existence of these types, repeated with constancy, seems to be clearly established by Schwartz's paper and corresponds perfectly to the writer's personal experience. But before sufficiently definite results could be obtained by Schwartz, Ostertag abandoned the objectively descriptive method by mixing those localization types with hypothetical interpretations which created new confusion. In any case, a pure study of the localization of gliomas is certainly no more justified than a purely histological study.

One may summarize the general results of the histogenetic period of glioma research as follows : two important glioma entities have been brought to our knowledge—the medulloblastoma by Bailey and Cushing (1925) and the cerebellar astrocytoma by Cushing (1931)—both discovered independently of the histogenetic principle. To this principle is due only the isolation of oligodendrogliomas by Bailey and Bucy (1929) ; these tumours form probably a histogenetic but certainly not a morbid entity. The consequent application of the histogenetic principle is not justified by clinical correlations as recognized by Cushing himself. It has created tremendous confusion as far as the pathology of gliomas is concerned, and provoked an enormous amount of work devoted to a forlorn hope. Innumerable histological details have been carefully described, but generally they are detached from the general pathology of the concerned neoplasms. They provoke arbitrary interpretations and cannot be used for the creation of a pathology of gliomas.

The Period of Complete Glioma Examination and Its First Results

Confronted with this disappointing situation and with an already extensive personal experience with gliomas, Scherer (1935*a*) came to the conclusion that the histogenetic principle as a basis of glioma research and classification could not be improved, but had to be given up for numerous reasons of technique and principle. Many errors of the histogenetic period of glioma research are caused by the blind faith of the authors in modern " specific " staining methods. It is obvious that there are no methods which are entirely specific in every circumstance, and thus that they have to be used with great reserve. This is especially true when methods worked out for normal brain tissue are applied to tissues the physico-chemical conditions of which are deeply modified ; this is undoubtedly the case in many brain tumours (Singer and Seiler, 1933). Furthermore, if these methods worked out for *normal* cell elements may give useful results for mature tumours, they cannot be expected to determine with certitude the nature of immature or anaplastic tumour cells. Based on the critical analysis of two cases of " glioblastoma multiforme ganglioides " (Foerster and Gagel, 1931) and of many ganglioneuromas * in the literature, Scherer's paper (1935*b*) gives ample proof that the use of specific stains in brain tumours of low differentiation does not lead to certitude, but to entirely arbitrary interpretations of their histogensis. Recently, Bailey (1938) admitted explicitly that he was previously " overly impressed with the specificity of silver methods." The best illustration of this fact is furnished by the frequent change of the classification of one and the same tumour encountered in the different papers of Bailey (1938) and Cushing (1932). The specific methods, although valuable auxiliaries for the solution of determined questions of detail (see Bailey's discovery of oligodendrogliomas), cause many more errors than progress when taken as a general technical basis of glioma research. Thus, a technical insufficiency already renders a histogenetic classification of immature gliomas impracticable.

Not only specific stains but also the possibilities of merely histological methods in general have been extremely over-estimated by authors who, although sometimes excellent histologists, were no pathologists. Histology is one of the methods of pathology ; it is not pathology. The fact of not reckoning with this fundamental principle—perfectly applied from Virchow until Ribbert—is undoubtedly much more responsible for the disappointing stage of modern glioma research than is the uncritical use of specific stains. The contemporary progress of neuro-surgery greatly favoured these tendencies. The study of biopsy material may be a practical necessity for neurosurgery; it never can be in itself an adequate method for pathological tumour research. Most modern investigators consider the use of small fragments as the normal method for glioma research to such a degree that they obviously examine even their necropsy material in the same incomplete way. This attitude explains why most modern papers do not even indicate whether necropsy or biopsy material has been studied, and why the authors use both mixed together, without indicating the proportion nor separating the conclusions drawn from both kinds of cases.

* In spite of this work, those cases continue to be quoted as " ganglion cell tumours" (Wolf and Morton, 1937).

The importance of this fact can hardly be overstressed ; Bailey and Cushing's classical description of the medulloblastoma group was obtained from a large amount of necropsy material, while their relatively poor and inadequate description of cerebral astrocytomas is obviously due to the extreme scarcity of necropsies. The rare glioma papers of the histogenetic period which studied necropsy material carefully (Carmichael, 1928 ; Davidoff and Ferraro, 1929 ; Cox, 1933 ; Deery, 1933) immediately stated facts which should have prevented a continuous use of biopsy material. Technique and ideas can never be separated from each other. The main problem of gliomas as well as of all other neoplasms is a growth and not a differentiation problem. As a glioma is not a dead phenomenon but an eminently living one, a dynamic point of view must try to study in the first place evolutionary stages and growth processes. A tumour is not a heap of cells independent from the tissue in which it grows. It only can be understood when studied in all its parts, especially in its growth zone and in its natural relationship with the tissue from which it originates. No specific staining of glioma fragments and no oil immersion can replace the complete study of the whole brain (Scherer, 1935*a*).

These considerations lead the author to the exclusive use of necropsy material for his glioma investigations and to the application of the following technique * of " complete " study of gliomas (Scherer, 1935*a*, 1938*b*, 1939*b*) :

After the whole brain has been fixed in formalin, it is cut into 15-mm. thick frontal slices. The slices showing a macroscopical modification are photographed. All slices containing the tumour from its frontal to its occipital end, with a large amount of surrounding macroscopically unchanged tissue, are imbedded in celloidin. As glioma growth very frequently is much more extensive than supposed from the macroscopic aspect (Scherer, 1939*a* ; 1940*a*), one has to study as many normal parts of the brain as possible. One, or sometimes several, thin but also very large slices are sacrificed for frozen and later on for paraffin sections, stained and impregnated by the different selective stains used in modern neuropathology. The celloidin blocks are cut quite deeply from both sides in order to obtain a kind of incomplete serial section study of the whole tumour and surrounding tissues. The ideal method, a real serial section study, is impracticable with a large material. The celloidin sections are always cut at 20μ in order to allow objective comparisons of cellularity, and stained with the Nissl, Van Gieson, and partially the Achucarro methods. A glioma being a cellular overgrowth, the necessity of a *nuclear* stain as a fundamental method must be emphasized ; large Weigert stained sections such as have been used recently by Waggoner and Löwenberg (1937, 1939) may give misleading results, even when completed by nuclear stains of some smaller fragments. To obtain the important link between macroscopic and microscopic pictures the Nissl stained sections are photographed in natural size, and the

* The great importance of both a really " complete " study and a very large material is illustrated by the fact that Kino (1935), who also tried to complete the merely cytological researches by a study of growth character, etc., reached no clear results : his technique was not complete enough and his material too small. Deery (1932) and Elsberg and Hare (1932) also felt the need of more complete techniques, but they also did not go far enough, and they applied their method to more limited questions.

extension of the tumour demonstrated in this way is carefully compared with the macrophotographs of the formalin-fixed brain slices. Then a careful microscopical study of all parts of the tumour is made; numerous photomicrographs are taken in order to allow objective control. The results are recorded in the following scheme : age, sex, duration of clinical symptoms, clinical diagnosis, brain's weight, presence or absence of brain swelling, exact localization, macroscopic aspects, mode of growth and extension, cytology, cellularity (determined by systematic counting : Scherer, 1940*b*), structural behaviour (Scherer, 1938*b*), behaviour of pre-existent tissues, mesenchymal structures, regressive changes, reactive changes, inflammation, particularities.

In that way, all the morphologic properties of a glioma are objectively recorded ; to characterize the tumour, none of them is given more weight than another. The principle of the author's glioma research (Scherer, 1939*b*) is that of all descriptive natural sciences. A glioma is a natural phenomenon. A natural phenomenon is characterized by the *whole* of its morphological and biological characteristics ; it would be easy, but arbitrary, to classify an animal according to the number of its teeth alone or a plant according to the form of its leaves only. It is not less arbitrary to subordinate study and classification of gliomas only to their cytology or to their localization. It is fantastic to base a classification not on observed facts but on interpretations (histogenesis instead of cytology, embryonal ætiology instead of localization : Ostertag, 1936).

The thorough application of this method of complete glioma examination takes a considerable time because of the large surfaces and great number of sections which must be studied in every case. This probably explains why it has not been applied until now by others, all the more as only the study of numerous cases could prove whether this tedious method would finally give worthwhile results or not. After the study of 130 cases during 8 years, the value of the method not only for pathological but even for clinical problems became obvious. This method will necessarily lead to a natural classification of gliomas deduced from facts instead of theoretical classifications imposed on facts, but not before several more hundreds of cases have been studied. As the natural classifications of all natural phenomena, that of gliomas certainly needs the collaboration of a large number of individuals using exactly the same methods of studying and recording, and this during long years. No new terminology will be proposed until this natural classification has been steadily established. As the only important principle of terminology is to avoid suggesting interpretations not supported by facts (see Ewing, 1936), the best would be a simple lettering and numbering of groups and subgroups (A1, 2, 3 ; B1, 2, 3). Meanwhile the generally adopted names will still be used with the clear understanding that they have no " histogenetic " significance. A striking example will show how the definition of the future natural groups will differ from the actual cytological definitions : the only diagnostic criterion of the cerebral astrocytoma of the cytologists is that it must be situated in the brain and composed predominantly by astrocytes. Scherer (1940*b*) quotes the extremely contradictory indications resulting from this definition in the modern literature about astrocytomas, and comes to the following definition : the tumours commonly called

cerebral astrocytomas are characterized by their diffuse character of growth, their generally enormous size, their moderate and uniform cellularity (except very old cases which may reach a considerable cellularity), the uniformly " amorphous " structure, the astrocytic character of a high but variable percentage of their cell elements, the histogenesis of a considerable percentage of which is doubtful ; the production of glial fibres in small or extensive areas ; the preservation of the pre-existent nervous parenchyma (nerve cells and fibres) in the tumour ; the tendency to microcystic degeneration of a type specific for astrocytomas ; the absence of necrosis ; the low vascularity without endothelial or adventitial proliferations ; the slow clinical course.

Let us now resume the preliminary theoretical and practical results obtained until now. A first series of systematic researches (Scherer, 1936 *a*, *b* ; 1937 ; 1938*b*) dealt with the finer proceedings displaying themselves in the growth zone of gliomas and their relationship with the pre-existent structures of the nervous system. Their study has been completely neglected by the modern glioma research, and the older papers had studied them in isolated cases only. It could be demonstrated that not only the spread but also the architectural development of gliomas is influenced to a high degree by the pre-existent tissue. Thus, a striking arrest of the growth of white matter gliomas at the grey matter (cortex, striatum) is very frequent, and certainly cannot be explained by mechanical factors (Scherer, 1936*a*). It creates the digitiform outline of many gliomas. Much rarer is the opposite, a systematical intracortical form of growth without invasion of the white matter. Nerve cells and fibres (Scherer, 1936*b*, *c*) play a prominent rôle in growth and structure formation of very numerous gliomas of quite different histology : frequently one observes that, as a glioma begins to invade the cortex or other masses of grey substance, the first manifestation of the neoplastic process is a collection of glioma cells around all or a great number of the nerve cells ; this perineuronal growth may occur in a precocious form (in a cortex otherwise relatively free from tumour cells) or as late phenomenon (in a cortex already heavily infiltrated by the tumour). After the disappearance of the nerve cells, these groups of tumour cells may persist and imitate the normal architectural pattern of the invaded region in a striking way. Extensive perivascular growth outside the Virchow-Robin spaces (Scherer, 1937) is also extremely frequent, and may, in rare instances, dominate the whole architecture of a glioma (Scherer and De Busscher, 1937). All these glioma structures conditioned by the pre-existent tissue are called " secondary structures " (Scherer, 1936*b* ; 1938*b*). They are infinitely more frequent and more important for the architecture of gliomas in general than the " proper structures," which are architectural patterns independent from the invaded tissue and thus probably conditioned by the intrinsic architectural properties of the neoplastic tissue. " Proper structures " dominate exclusively the architecture of ependymomas, which show a purely expansive type of growth. The structural behaviour varies greatly from one glioma to the other and in different stages of the growth of one and the same case (Scherer, 1938*b*). Thus, certain gliomas show always an " amorphous " (structureless) arrangement of their cells, although nerve cells and fibres are perfectly preserved in the midst of

the tumour. This behaviour is encountered, for instance, in all typical cerebral astrocytomas ; the same tumours may show extensive evolution of secondary structures when dedifferentiation into " glioblastoma " occurs in them (Scherer, 1940*b*). Other more frequent gliomas are characterized by a primary growth in the form of secondary structures, followed by an " amorphous " stage and finally by various " proper structures." The characteristic differences of the structural development in gliomas can only be considered as an expression of fundamental biological differences of the tumours themselves, and thus are an important morphological characteristic of them.

These findings raise important questions of pathogenesis : are the curious secondary structures due to a progressive neoplastic transformation of the pre-existing glia cells (for instance, the satellites of nerve cells, the perivascular glia cells), or to a selective migration of glioma cells towards these pre-existing structures ? The first interpretation corresponds best to the facts observed and has thus been repeatedly defended since Storch (1899) ; but it is in opposition with a still dominant fundamental dogma on the growth of neoplasms. The second interpretation would put the problem of the causes of this curious " neuronotropism " of glioma cells. It certainly cannot be interpreted—as could perhaps be the perivascular growth—by nutritional necessities. Obviously those problems cannot be solved by morphologic methods alone ; but they should be attacked with the help of the new methods allowing an experimental glioma research (tissue culture, experimental gliomas by carcinogenetic agents).

Another question of pathogenesis (Rindfleisch, 1886 ; Henneberg, 1897 ; and Landau, 1910) seems to be resolved already by morphological methods : namely that of the primary diffuse growth character of certain not infrequent brain tumours, especially of so-called cerebral astrocytomas. Scherer (1940*b*) applied his method of " complete " glioma examination to this group with the following result : the tumours commonly called cerebral astrocytomas are always primarily diffuse gliomatous overgrowths, comparable to lymphosarcomatosis. This fact has been proved by the observation of astrocytomas from patients who died accidentally at a time when they were just beginning to give rise to symptoms, which already showed entirely diffuse neoplastic overgrowth of uniformly low cellularity in all its parts. One never finds in astrocytomas systematized differences of cellularity which would suggest that " the growth starts in an area which is the nucleus of the tumour," as supposed by Waggoner and Löwenberg (1937). Furthermore, Scherer confirms for astrocytomas an old suggestion made by Golgi (1875, 1884) : the cortical parts of these diffuse tumours are afibrillar (except the subpial layer), even when their white matter parts are highly fibrillary. That corresponds exactly to the local differences presented by the normal astrocytes and those found in reactive proliferations. This behaviour cannot be explained by tumour cells coming from the white and invading the grey matter or vice versa, but only by neoplastic proliferation of the local elements which maintain their fibrillar or afibrillar character.

But the method of complete glioma examination already has given results of

practical interest. The cerebral astrocytomas such as were studied during the histogenetic period were one of the groups which had given rise to most contradictory opinions on questions of great practical importance : their frequence, their diffuse or circumscribed character, their ability for anaplastic degeneration and the eventual causal relationship of this degeneration with surgical interventions (Tooth, 1912 ; Globus, 1931 ; Müller, 1933 ; Scheinker, 1938*a*) are only some much discussed points, a clear answer to which must have therapeutic consequences. Scherer (1940*b*) stated the following facts : of 125 gliomas, only five " pure " cerebral astrocytomas have been encountered ; 13 other cases of this group include microscopically (four cases) or macroscopically visible areas of glioblastoma. Their whole morphology and the clinical aspect prove that these are astrocytoma derivatives. Not a single circumscribed cerebral astrocytoma has been found : all were primarily diffuse growths of generally enormous size. There are cerebral astrocytomas which show no dedifferentiation into glioblastoma at necropsy, even after a duration of 10 years, in spite of operations performed many years before death; the majority shows such a dedifferentiation without any operation. This is a striking proof that the surgeon is not responsible for this " malignant degeneration," contrary to some opposite opinions defended previously after the usual study of fragments of tissue. Those " secondary " glioblastomas have to be strictly separated from the " primary " ones ; the most striking difference on necropsy material is that the former show no or comparatively small necrosis (not over about $\frac{1}{10}$ of the living tumour tissue), while in the latter the necrotic areas are almost always more extensive than the living tumour tissue. Small cystic degeneration of the type encountered in astrocytomas is not found in primary glioblastomas. Once more facts prove the error of an abstract doctrine, namely that degenerative lesions have no importance for the classification of tumours (Bucy and Gustafson, 1939). The clear separation of primary and secondary glioblastomas renders also the clinical and biological differences much clearer : the cases of " glioblastomas with long clinical evolution " quite probably are a result of incompletely examined astrocytoma derivatives. The evolution of none of Scherer's (1940*b*) primary glioblastomas reached one year, in most cases it was beyond 6 months.

The new definition of cerebral astrocytomas as primarily diffuse growths join them into one group with the numerous isolated cases published under such names such as " gliomatosis cerebri " by Landau (1910), Angyan (1912), Bielschowsky (1915), Cassirer and Lewy (1923), Schwartz and Klauer (1927), Foerster and Gagel (1934), Santha (1936), and most completely studied by Nevin (1938 *a*, *b*). These cases have all the growth characteristics of the classical cerebral astrocytomas, such as have been elaborated since Virchow, and also their clinical behaviour ; most authors did not dare to classify them because of the existence of numerous non-astrocytic elements. The excellent objective description of Nevin makes it unquestionable that these are dedifferentiated diffuse astrocytomas.

For the primary glioblastomas the complete examination shows at least two, probably more, definitely distinct pathological (not histological) entities. The

exact limitation of these groups and their eventual clinical correlation needs still further study.

In another systematic study devoted to a problem of practical interest, Scherer (1938*c*) studied the frequency of gliomas having variable histological structure. Almost all authors of the histogenetic period consider implicitly or explicitly the uniform structure of gliomas as established to such a degree that their whole method—that of the study of arbitrarily taken fragments of tumour tissue—is based upon this doctrine. Only some more careful modern workers (Carmichael, 1928 ; Davidoff and Ferraro, 1929 ; Cox, 1933 ; Deery, 1933) had stated with necropsy material that mixtures of different cytological glioma " entities " in one and the same case are not infrequent and must cause errors when examined as operation material. Thus they confirm what already Virchow (1863–1865), and after him many others, had seen. However, the practical importance of those combinations depends obviously on their frequence, and this could only be determined by " complete " examinations : these proved that definite mixtures of recognized cytological entities occur in about 40 per cent. of all gliomas, and that in about 26 per cent. " benign " and " malignant " types are mixed. This frequence has been contested by authors who have not applied the method of " complete " glioma study ; as the percentages discovered exclusively depend upon the quantity of tumour tissue examined, Scherer's percentages can only be contested by an equally complete study of equal numbers of cases. The sole histogenetic " entity " which I have never seen with any mixture is the medulloblastoma. It becomes obvious from these statements that conclusions drawn from biopsy material should be considered with the greatest possible diffidence.

Finally, the growth forms of gliomas have been systematically studied from a practical point of view (Scherer, 1939*a*, 1940*a*). For all tumours, the anatomical features most important for the clinician and surgeon are localization and growth type. They have a direct and decisive influence on the possibility of complete extirpation. The cellular aspect of a neoplasm can only give indirect indications, and that only if its constant correlation with a given type of growth is well established, e.g. for carcinomas. The pathology of gliomas, however, is still far from this stage. The growth type of gliomas has received so little attention in modern papers that even the words " growth zone " are entirely lacking in most of them. In view of the neurosurgical purposes of most of these papers, this omission is astonishing. The sole connected problem carefully studied is that of glioma metastases in the ventricular system (Russell and Cairns, 1930 ; Cairns and Russell, 1931 ; Bodechtel and Schüler, 1937 ; Hasenjäger, 1938) with the result that those metastases are not specific to medulloblastomas, but rarely may occur also in almost every type of glioma. Nelson (1936) even described a small intravertebral metastasis of a medulloblastoma. As the previous communications (e.g. Mittelbach, 1934) on gliomas with metastases outside the nervous system are more than questionable, Nelson's case would be the first authentic instance of such a metastasis.

Scherer's statements may be resumed as follows : only one rare type of

glioma, the ependymoma, shows the purely expansive growth which alone gives good chance for extirpation without recurrence. All the others are infiltrative without exception, and thus realize the essential morphological criterion of malignancy (Ewing, 1928). However, in many cases (about 30 per cent. of all gliomas, including cerebellar astrocytomas, medulloblastomas, certain oligodendrogliomas, many glioblastomas) the zone of growth is so narrow that it coincides approximatively with the macroscopical visible limits and thus may give a chance for complete removal, all the more as secondary factors (arrest of the tumour at the cortex, etc., marginal degenerative lesions) may strengthen the circumscribed character. But the majority of gliomas is much more extensive than the macroscopical aspect leads us to suppose : about 60 per cent. have a more diffuse character with a widespread zone of growth, the diffuse nature being either secondary (about 35 per cent.) or primary (about 25 per cent., including all astrocytomas of brain hemispheres and brain stem). About 10 per cent. of all gliomas—most of them belonging to the glioblastoma group—are primary multicentric growths, half of which are macroscopically visible as multiple tumours. This fits in fairly well with the percentage of multiple gliomas obtained by Courville (1936), while incomplete study may give either too low (Bailey and Cushing : 2 on 412) or too high percentages (Globus and Strauss, 1925 ; 6 on 17 ; Brandt, 1934 : 4 on 20 cases), the latter probably because the unique character of a glioma with digitiform shape had not always been recognized. On the whole, identical " histogenetic " groups include gliomas of quite opposite behaviour of growth. The most " mature " types (cerebral and pontine astrocytomas) are the most infiltrative and thus the harder to extirpate completely.

Infiltrative and destructive growth are by no means synonymous in gliomas and this is of clinical importance. A long preservation of nerve cells and nerve fibres in the midst of the tumour is not specific to astrocytomas, but is also encountered in a lesser degree in many glioblastomas. The ignorance of this fact known in principle since 1895 (Stroebe) and the subsequent erroneous interpretation of these pre-existent nerve cells as tumour cells is one of the obvious reasons why certain authors find so many " gangliogliomas," " glioneuromas," etc. (Globus, 1938), while others have not seen them at all or quite exceptionally. The other is the too generous application of the term " neuroblast " to cells whose neuroblastic character is at least unproven. The writer entirely confirms Cox's statement that the neuroblast is particularly difficult to identify. Cox also gives a very comprehensive study on the rôle of pre-existent glia cells included by the glioma.

On the whole, the extensive use of the method of " complete " glioma examination seems to be justified by the first results obtained, especially if one considers that we are only at the beginning of these researches. Their purpose is to replace merely academic investigations on cytologic questions by a living pathology equally useful to both clinician and pathologist. In many respects, they take up again the study of gliomas where it stood before the histogenetic period, but in a more systematic way : a much larger material than in the classical researches is studied with a much more complete method, and the

enormous progress made during the last 30 years by both neuropathology and cancer research are applied to the pathology of gliomas.

Some Particular Aspects of Glioma Pathology

There remains a certain number of particular aspects of glioma pathology not yet discussed in this review. We will not go here into details about the lesions occurring in glioma brains outside of the tumour. They consist in hæmorrhages or necroses, brain swelling or brain œdema, and in cysts. Hæmorrhages in the brain stem are frequent in brain tumours of quite different location : Rosenhagen (1932) observed them in 10 out of 16 cases. Bannwarth (1935) had the impression that temporal tumours produce these lesions more frequently than others. Moore and Stern (1938) emphasized the occurrence of hæmorrhagic infarction of the visual cortex alone or together with hæmorrhages in the brain stem. Bodechtel and Döring (1938) observed also softenings in other locations (basal ganglia, diencephalon, etc.). While Moore and Stern believed that surgical procedures have no pathogenetic significance, Kaufmann (1938) defends the opposite opinion. All authors agree that these lesions must be considered as consequences of the increased intracranial pressure and its effects on the cerebral circulation. Less clear is the pathogenetic relation between brain swelling and glioma. While the histology of brain œdema has recently been studied by Greenfield (1939), the ætiology of this important phenomenon has given rise to numerous hypotheses but to few really established facts. Extra-neoplastic cysts in the surrounding brain tissue have been described for cerebellar astrocytomas (Bucy and Gustafson, 1939).

The literature contains innumerable indications, but no systematic studies on degenerative lesions in gliomas. They cannot be discussed in this paper. It may be presumed that large cysts are frequent in cerebellar, but relatively rare in cerebral astrocytomas and ependymomas. Extensive necroses are specially characteristic of primary glioblastomas, but occur also in ependymomas, although never in pure cerebral astrocytomas. Further studies unhampered by histogenetic tradition are certainly needed.

Two other questions have still to be discussed because of their interest for general pathology. One concerns the occurrence and significance of mesenchymal stroma and vascular proliferations in gliomas. There are definite differences of vascularity in different types of gliomas, but beside the careful work of Elsberg and Hare (1932), few systematic studies have been devoted to this question. Recently the benzidine stain has been applied with some success to this problem (Sahs and Alexander, 1939 ; Bertha, 1939). It shows that the degree of vascularity is not proportional to the rapidity of growth : while " astrocytomas " have a very low vascularity, the usually slowly growing " oligodendrogliomas " are extremely rich in capillaries. However, more extensive studies unimpeded by the histogenetic schemes are greatly needed. Those who recorded objectively the facts were always impressed by the importance of mesenchymal and vascular proliferations especially encountered in so-called glioblastomas (Tooth, 1912 ; Bertrand and Medakowitch, 1922 ;

Penfield, 1931 ; Scherer, 1933, 1935*c* ; Torkildsen, 1935 ; Bertha, 1939) and emphasized their important rôle for the whole of the morphologic characteristics of these tumours. The special angioplastic proliferations, contrary to Bailey and Cushing (1925), Deery (1932), and others, cannot be considered as banal, reactive vessel proliferations, at least not their glomerular type (Scherer, 1935*c*): they are not seen outside of these gliomas. Penfield's (1931) opinion that they are the essential histological characteristic of glioblastoma multiforme does not correspond entirely to facts, in so far as these formations rarely may appear also in other types, especially in astrocytomas, together with dedifferentiation —(Scherer, 1940*b*). In very pronounced form these angioplastic proliferations have always been observed in cases with extremely rapid evolution (Scherer, 1935*c*). This and the curious fact that they precede the growth of the tumour, growing from the uninvaded tissue towards its edge (Scherer), give to them a biological significance which has not been clarified until now. In spite of the numerous mitoses found in these proliferations, it is neither proved nor excluded that they are a real part of the neoplastic growth process (" angiogliomas," Roussy and Oberling, Holtzer, 1939). They too certainly deserve further careful research.

Still less solved is the important problem of combined cases of glioma and mesenchymal sarcoma, as far as it is not interpreted as a simple coincidence, but either as primary combination or as " reactive glioma " around a primary sarcoma. These cases have been described by Merzbacher and Uyeda (1910), Wohlwill (1911), Cornil and Robin (1922), Pines (1922), Neubürger and Singer (1926), Gulotta (1933), Bailey and Ley (1934), Marburg (1935), Spatz (1938). Most authors consider their cases as primary meningeal sarcoma with secondary glioma, while Bailey and Ley defend the opposite opinion for their case. The writer examined three (unpublished) cases of this kind and had also the impression that the gliomatous tumours probably were secondary to the meningeal neoplasms. This question has a great theoretical importance : the proof of a causal dependence of the gliomatosis upon the meningeal tumour would mean that the latter provoked the former by " induction." The importance of this question, the doubtful character of some of the published cases, and the enormous difficulty of correct interpretation of such tumour combinations (see Saphir and Vass, 1938) should impose the greatest possible caution before definite conclusions are drawn from these curious cases.

Ætiological Problems. Experimental Glioma Research. Comparative Pathology of Gliomas

The same reserve, always necessary when ætiologic conclusions have to be reached by morphological methods, is necessary in the rare but important cases of combination between true glial neoplasms and lesions belonging to the group of multiple and diffuse sclerosis or " disseminated encephalomyelitis." In some cases of acute " multiple sclerosis " highly atypical glial cells of neoplastic appearance have been observed (Creutzfeld, 1923 ; Peters, 1935 ; and others), and Hallervorden (1930) describes several cases where the definite differential

diagnosis between a glioblastoma and an acute multiple sclerosis was not possible. Scherer (1938*a*) described a case where a typical disseminated encephalomyelitis and multiple tumours of the type of " glioblastoma multiforme " were combined in such a way that the direct evolution of the neoplasm from the encephalitis was very probable. Schöpe (1938, 1939) published two similar cases, but interpreted them in a way (Hodgkin's disease of the brain without manifestation in other organs !) which was quite unsupported by the facts described. The writer had the opportunity of studying sections of Schöpe's first case and must state that it certainly has nothing to do with Hodgkin's disease, but belongs clearly to the group of cases here discussed. Their great importance is that they suggest the possible rôle of extrinsic ætiologic factors for the ætiology of gliomas. It must be mentioned in this connection that Russell (1932) described curious " intranuclear inclusion bodies " as very frequent in glioblastomas and insists upon their resemblance with such inclusion bodies described in virus diseases.

This has to be emphasized because until now almost exclusively intrinsic factors, or, more precisely, an ætiology by displaced embryonal cell nests, have been taken in consideration. It would be difficult to find a more striking example of doctrines influencing the judgment of investigators to such an extent that they take for granted a hypothesis unsupported by seriously established facts. Since the last century authors always discussed this hypothesis under the influence of Cohnheim and Ribbert's theory relating all neoplasms to such slumbering embryonal mother cells. The fact that certain gliomas rise in brains with tuberous sclerosis (Bielschowsky, 1924 ; Globus, Strauss and Selinsky, 1932) proves nothing for the enormous majority of gliomas where the slightest sign of tuberous sclerosis cannot be found : the author has not encountered one single case of this coexistence in 130 gliomas the brains of which were completely examined.

As mentioned above, Ribbert (1918) first presented this hypothesis as a well-established fact for all gliomas, but without any proof. Since that time many authors consider this theory as sufficiently established for building their whole system upon it, while others state that " the evidence is practically conclusive that these tumours (i.e. gliosarcomas) arise from once adult cells, and that their structure and behaviour are determined by anaplasia and not by embryonal qualities " (Ewing, 1936). Ostertag still tries, in 1936, to accredit the " dysontogenetic " hypothesis not only for some but for all gliomas, to " explain " in this way not only their ætiology but even their whole histology, localization, and biological behaviour, and calls the desultory and illogical result a " natural classification explaining location, extension, and structure." Ostertag simply repeats the facts already discussed last century (see Stroebe, 1895 ; Saxer, 1902, and many others), and adds the supposition that the identical localization, repeated with astonishing constancy by numerous gliomas, corresponds to areas which are predestined, by the embryonal development of the nervous system, to local malformations. If this may be true for some cases, such as medulloblastomas, the enormous majority, by their great extension, does not allow recognition of the point of origin. It is therefore impossible to compare

its location with that of the incriminated embryonal disturbance. Even if such a local congruity could be demonstrated, it would be no proof for the causal relationship between developmental troubles and glioma growth, no more than the well-known predominant localization of the patches of multiple sclerosis in the periventricular zones proves for such an embryonal relation. Somewhat more interesting would be the evidence of local malformations in given cases of gliomas, but Ostertag describes not one similar case. His interpretation of the frequently very pronounced overgrowth of mesenchymal tissue in gliomas as " primarily abnormal mesenchymation " of the area concerned is not supported by facts (Scherer, 1933, 1935*c*). The frequently encountered opinion that diffuse gliomatoses ought to be considered as " dysontogenetic " disturbances (Hallervorden, 1936) is not supported by any facts. An extrinsic factor able to stimulate neoplastic growth of a circumscribed area cannot be considered *a priori* as being unable to have the same effect in a large area. On the whole, Ostertag brings not a single new fact supporting seriously the old hypothesis which becomes a real anachronism in a period where the enormous rôle played by extrinsic factors (carcinogenic agents, viruses) in the ætiology of neoplasms has been proved in a peremptory manner. There is no reason for considering the ætiology of gliomas outside of that of other neoplasms : " Tumours are highly conditioned diseases dependent upon a concatenation of factors—heredity, age, chemical irritation, etc., etc.," says Rous (1936). This should always be borne in mind, also for the much discussed but unsolved question of the " traumatic origin " of gliomas, defended by some (Beneke, 1932 ; Marburg, 1934, and others) and refuted by others (Fischer-Wasels, 1932) with the same emphasis ; for the " hereditary brain tumours " such as described by Hallervorden (1936) and others ; familial occurrence of gliomas, as of all neoplasms, does not prove more for their predominantly hereditary character than familial occurrence of tuberculosis (Rous, 1936).

After all the fanciful ætiological considerations filling the glioma literature until the last years, two recent important advances begin to put facts in the place of hypotheses : the appearance of the comparative pathology of gliomas, and that of experimentally produced gliomas. The first shows clearly that gliomas are relatively frequent in certain animals, extremely rare in others. The frequence of gliomas in the dog has been established especially by Hjärre (1924, 1926) and by Milks and Olafson (1936). The latter find primary brain tumours in 4 per cent. of their necropsies in dogs ; from these 10 cases, 5 are classified as gliomas or ganglioneuromas (one of which was situated in the cervical cord), one as choroid papilloma, four as perithelial sarcomas. Unfortunately there is no detailed description allowing a discussion of these diagnosis. Whether the extremely high percentage they observed will be confirmed in the future or not, the relative frequency of gliomas in the dog seems already established. According to Grün (1936), there even seems to be a predominance for certain races (Boston terriers, English setters, etc.). In addition to dogs, horses and chickens (see Jungherr and Wolf, 1939) have been frequently found to harbour gliomas. On the other hand, they must be extremely rare in mice (Slye, Holmes and Wells, 1931), and certainly are not frequent in

monkeys.* Scherer has not seen a single case on 152 necropsies of monkey brains. From Fox's (1923) monograph as well as from Hamerton's (1934–1938) reports, it would seem that captive wild animals only rarely show brain tumours. However, systematic researches on this question are needed. Jungherr and Wolf (1939) give a complete, critical, and very comprehensive review of the whole literature and try to recognize, from the mostly very poor histological descriptions, which tumour type was present. They have the impression also that in animals the groups of astrocytoma and glioblastoma are more frequent than other varieties. They give the first detailed description of a definite type of lobulated, multiple brain tumours rich in connective tissue, but predominantly formed by astrocytes, which seem to be characteristic of the chicken. Comparative pathology of gliomas is only at its beginning, but its first statements are already important for experimental glioma research.

Since the discovery of the modern carcinogenetic agents numerous investigators used them in order to obtain experimental gliomas, and most of them without success. Some of these failures have been published (Oberling, Guérin and Guérin, 1936 ; Askanazy, 1937 ; Bertrand and Grüner, 1938 ; Peers, 1939), many have not, as for instance the author's personal experiments on 70 white rats and four dogs. Weil (1938) published what he considered as being experimental gliomas in white rats, but his description and illustrations make it unlikely that the obtained tissue proliferations were real neoplasms. Finally, Seligman and Shear (1939) obtained by intracerebral implantation of pellets of methylcholantherene in 20 male C_3H mice, 11 gliomas and two fibrosarcomas after 8 to 17 months. The high percentage of positive cases and the absence of spontaneous brain tumours in mice exclude any doubt about the causal relationship with the carcinogenetic agent. Description and illustrations make it absolutely sure (1) that undoubted neoplasms of sometimes enormous size were obtained, (2) that most of them showed a morphology identical with human " gliomas," and (3) that different histological types are represented. From the illustrations there is no doubt that tumours from glioblastoma and from astrocytoma type have been produced, while some of the other cytological diagnoses (made by Alexander) are not supported by the illustrations. However, this has merely a secondary interest. The essential fact is the proof that typical gliomas can be provoked by carcinogenetic agents. This discovery will be a turning-point of glioma research : it marks the end of the fanciful ætiological speculations about " congenital malformations," for the proof is established that gliomas can be produced at will in an animal which develops no spontaneous gliomas. Whether the mouse brain contains " embryonal cell rests " or not, they never do form tumours without methylcholantherene. This does not exclude the coexistence of constitutional or racial factors ; their existence seems to be indicated both by the great differences in the spontaneous occurrence of gliomas observed in different animals and by the failures of the attempts to produce them in rats. So far, comparative pathology and experi-

* The literature contains a short paper about a gliosarcoma in one *Cercopithecus Anubis* (Sellheim, 1936), but there is no sufficient description to judge whether this was a glioma or not.

mental production of gliomas only prove that gliomas, as well as all other neoplasms, must have different causes and rise only by a concatenation of events. The enormous importance of Shear and Seligman's discovery is to open the way to a systematic experimental glioma research. One may reasonably hope that a comprehensive and systematic use of this discovery and perhaps also of tissue culture, no longer impeded by merely histological and " histogenetic " problems, will bring the solution of many pathogenetic, ætiological, and even therapeutic problems which could not be solved by morphological methods alone.

Conclusions

The historical evolution and the actual stage of the pathology of gliomas give worthwhile indications for future glioma research. It is obvious that the pathology of gliomas is far from being established and that problems of pathogenesis and ætiology could not be seriously studied until now because of the lack of adequate methods. The evolution of glioma research shows clearly that unilateral investigations on cellular aspects, if detached from the other morphological aspects of gliomas, lead to confusion and to arbitrary classifications in contradiction with the facts. Two main purposes and the appropriate ways for their solution are clearly indicated to future investigators.

The first is the creation of a modern pathology of gliomas by a careful and complete objective description of facts independent from doctrines and preconceived classifications. A natural classification will necessarily be the final result when all the morphologic properties of a sufficient number of gliomas shall have been studied in a really complete manner. No biopsy material can be used for these studies. This pathology and a final natural classification of gliomas are greatly needed by both pathologist and clinician. They also have to furnish solid bases and exactly formulated problems for experimental work.

The second main purpose of future glioma research has become realizable by the recent production of experimental gliomas by carcinogenetic agents. The numerous pathogenetic and ætiological problems of glioma pathology cannot any longer be studied only with morphological methods, inadequate for their solution. They ought to be attacked by the systematic application of the method of experimental gliomas, perhaps in combination with tissue culture and comparative pathology.

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*A Method of inducing Frustration in Human Subjects and Its Influence upon Palmar Skin Resistance. G. L. Freeman. 117.

Limits of Toleration for Simultaneity.—Further investigations with new apparatus on the limits of toleration in simultaneity are described, with analysis of errors and determination of their limits. Experiments show effects of speed, differences for simultaneity of two stimuli, and effect of a warning signal. (H. de P.)

Configurational Properties.—Naïve subjects were free to change material consisting of 40 geometrical figures so as to produce what they considered " good configurations." Results show that closure and symmetry are on the whole considered " good " by these subjects. This is in line with the general conception of " good " in art and æsthetics and also with the prevalence of these properties in nature. (H. de P.)

Humour and Laughter.—Difficulty of analysis due to variety in laughter itself. Author suggests following formula : " Laughter occurs when a total situation causes surprise, shock, or alarm, and at the same time induces an antagonistic attitude of playfulness or indifference." This idea is elaborated with reference to the laughter of children, particularly when induced by tickling, and of adults. The importance of incongruity in humour is stressed. It is only in children that laughter is purely an expression of joy and playfulness. (H. de P.)

Experimental Analysis of Motor Skills.—A review of theories on individual variations in motor skills with data from previously unpublished experiments. Further experiments will be reported later. (H. de P.)

Suggestibility.—Olfactory and visual tests for suggestibility were made on subjects suffering from four types of mental disturbance : (1) asthenic (subvalid) ; (2) hysteric (subsolid) ; (3) manic depressive (substable) ; and (4) intellectual deficiency (subcapable). Intellectual defectives were found to be the most suggestible and hysterics next. Manic-depressives were the least suggestible, and it was noted that in this group the pyknic bodily type predominates. A high correlation was found in the subjects' suggestibility in the two kinds of test used. (H. de P.)

Induced Frustration and Palmar Skin Resistance. — Pavlov's method of experimenting on conditioned reflexes in dogs has been adapted for use on human beings in order to investigate the effect of frustration. It was found to produce breakdown of specific differentiations with concurrent rise in general bodily excitement, indicated by decreased palmar skin resistance. (H. de P.)

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Quelques Terminaisons des Délires Chroniques. Suspension et Réintégration du Délire ; Degrés divers de Réadaptation Sociale ; Processus de Normalisation. (Results of chronic delirium ; suspension of reintegration ; degrees of readaptation ; process of normalization.) J. Vié. 461.
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Pensée Affective et Psychopathologie. (Affective thought and psychopathology.) J. Burstin. 557.
Automatisme et Hypertonie de Nature Psychomotrice. (Automatism and hypertonia of a psychomotor character.) J. Euzière, E. Fassio, and R. Lafon. 575.
L'Assistance auz Aliénés en Algérie depuis le xix^e Siècle. (Assistance to mentally afflicted in Algeria since the nineteenth century.) M. Desruelles and H. Bersot. 578.

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Vol. 42. No. 6. December 1939.

*Preliminary Analysis of Functions of the Temporal Lobes in Monkeys. H. Klüver and P. C. Bucy. 979.
Histopathogenesis of Cerebral Abscess. F. A. Carmichael, J. W. Kernohan, and A. H. Adson. 1,001.
*A Roentgenographic Sign in Cases of Tuberous Sclerosis of Brain (Multiple "Brain Stones"). P. I. Yakovlev and W. Corwin. 1,030.
*Acute Anterior Poliomyelitis (Heine-Medin Disease ?), with Unusual Cerebral Manifestations: Clinical and Pathologic Report of a Case. R. B. Richter. 1,038.
Sodium Diphenyl Hydantoinate in Treatment of Convulsive Seizures: Toxic Symptoms and their Prevention. H. H. Merritt and T. J. Putnam. 1,053.
*Pallidofugal Fibers in the Monkey. S. W. Ranson and M. Ranson. 1,059.
Dementia Paralytica: Effect of Continuous Intensive Therapy with Tryparsamide and Bismuth on Cerebrospinal Serologic Reactions and Frequency of Relapse. G. W. Forman. 1,068.
Cells of Origin of Fibers of Corpus Callosum: Experimental and Pathologic Observations. L. J. Pines and R. M. Maiman. 1,076.
*Diffuse Progressive Leukodystrophy in the Adult, with Production of Metachromatic Degenerative Products (Alzheimer-Baroncini). L. van Rogaert and A. Dewulf. 1,083.
*Sweat Secretion in Man. V. Disturbances of Sweat Secretion with Lesions of the Pons, Medulla, and Cervical Portion of Cord. C. F. List and M. M. Peet. 1,098.
Case Reports.
Cerebral Calcification in a Case of Chronic Progressive Chorea. D. M. Lipshutz. 1,128.
Resection of Longitudinal Sinus Posterior to the Rolandic Area for Complete Removal of Meningioma. G. L. Maltby. 1,135.

Functions of Temporal Lobes.—The behavioural effects of removal of both temporal lobes, including the uncus and the greater part of the hippocampus, were studied in macaques. The monkeys exhibited the following symptoms: (1) forms of behaviour which seemed to be indicative of "psychic blindness"; (2) strong oral tendencies in examining available objects; (3) a strong tendency to attend and react to every visual stimulus; (4) marked changes in emotional behaviour; and (5) an increase in sexual activity. (R. M. S.)

Roentgenographic Sign in Tuberous Sclerosis.—Attention is drawn to a roentgenological manifestation of tuberous sclerosis of considerable diagnostic significance, namely, multiple disseminated areas of intracerebral subcortical calcification—the multiple "brain stones." (R. M. S.)

Acute Anterior Poliomyelitis.—A case of poliomyelitis of unknown origin is described which is remarkable for the associated diffuse encephalitis and inflammatory changes in the blood vessels of the nervous system. (R. M. S.)

Pallidofugal Fibres.—Large, deeply staining, myelinated fibres arising from the cells of the medial division of the globus pallidus form the ansa and fasciculus lenticularis. The pallidohypothalamic tract consists of fibres which run ventomedially into the hypothalamus, passing either through the fornix or over its dorsomedial surface. Finer striofugal fibres, which probably arise in the caudate nucleus and putamen and possibly also in the lateral division of the globus pallidus, can be traced to the substantia nigra and the subthalamic nucleus. The cells of the medial division of the globus pallidus are larger and more angular than those of the lateral division, and they disappear after interruption of the fibres of the ansa and fasciculus lenticularis. Monkeys in which the ansa and fasciculus lenticularis have been interrupted bilaterally show no gross disturbance of movement. The movements, however, are slow and lacking in spontaneity. The faces of these monkeys are immobile and masklike. (R. M. S.)

Diffuse Progressive Leukodystrophy.—The adult form of diffuse sclerosis may have a particularly long evolution (seventeen years in the case reported) with a clinical picture, at the same time, of pseudoparalysis and athetosis. The clinical diagnosis is always difficult. It is based on the association of mental disturbances with an epileptic, spasmodic component, and a progressive cerebellar and athetotic evolution with gross disorders of speech, ending in loss of articulation. In the case reported here the disease was characterized pathologically by a metachromatic disintegrative process. It presents, otherwise, all the histologic characteristics of the heredodegenerative forms of leukodystrophy, in which the disintegration predominates over the proliferative and exudative vascular process. (R. M. S.)

Sweat Secretion in Man.—Sweating disturbances are described in eighteen patients with lesions of the pons, medulla oblongata, and cervical part of the cord. The authors attempt to outline the probable course of the cerebral vegetative pathways which may also mediate impulses for thermo-regulatory perspiration. (R. M. S.)

Vol. 43. No. 1. January 1940.

*Action Potentials of Muscles in "Spastic" Conditions. P. F. A. Hoefer and T. Putnam. 1.
*Results of Experimental Removal of Pineal Gland in Young Mammals. L. Davis and J. Martin. 23.
*Modification of Gudden Method for Study of Cerebral Localization. A. Brodal. 46.
*Studies in Multiple Sclerosis: Serum Enzymes. C. H. Richards and H. G. Wolff. 59.
Effect of Phenobarbital on the Mentality of Epileptic Patients. E. Somerfeld-Ziskind and E. Ziskind. 70.
*Relation of Ventricular Asymmetry to contracting Intracranial Lesions. J. S. Robertson and A. E. Childe. 80.
*Relation of Anoxemia to Early Activity in the Fetal Nervous System. W. F. Windle and R. F. Becker. 90.
A Clinical Study of Anxiety Attacks. H. L. Kozol. 102.
*Congenital Demyelinating Encephalopathy. R. P. Mackay. 111.
*Probable Topographic Relations of the Sleep-Regulating Center. J. H. Globus. 125.

Case Reports.

*Ventriculographic Diagnosis of Agnesis of the Corpus Callosum. A. Kunicki and J. Chorobski. 139.

Action Potentials of Muscles.—The action potentials of twenty-four patients with spastic conditions were investigated and a number of new features described. (R. M. S.)

Experimental Removal of Pineal Gland.—It may be postulated, on the basis of the results here presented, that the pineal gland has a glandular function, probably endocrinal, early in life in mammals and that its function exerts through a yet undescribed process an influence on the sexual and somatic development of the immature animal. (R. M. S.)

Gudden Method for Study of Cerebral Localization.—The author describes a modification of the Gudden method for investigation of localization within the central nervous system. It has the advantage of a practically total loss of the affected cells. (R. M. S.)

Multiple Sclerosis: Serum Enzymes.—The experiments reported here are not considered as having disproved the theory that an abnormal enzyme may be involved in the pathogenesis of multiple sclerosis. (R. M. S.)

Ventricular Asymmetry and Contracting Intracranial Lesions.—When an atrophic lesion occurs in one cerebral hemisphere after the period of rapid growth of the skull there may result a shift of the septum pellucidum and third ventricle toward the side of the lesion. Such a shift does not necessarily indicate the presence of adhesions. It is modified by compensating collections of fluid, as in cases of porencephaly, subarachnoid and intracerebral cysts, and enlargement of the lateral ventricle on the side of the lesion. Adhesions may accentuate a shift by the prevention of subarachnoid collections of fluid or porencephaly. The amount of shift of the ventricular midline appears to be dependent on the uncompensated loss of cerebral substance. It is doubtless also dependent to some extent on the site of the lesions. As the exact extent of the lesion cannot be accurately estimated, comparative estimates for different sites are impossible. During the period of rapid growth of the skull the presence of a lesion resulting in the loss of cerebral substance causes a relative reduction in the rate of growth of the ipsilateral side of the skull. In an asymmetrical skull which is not the result of an early cerebral lesion it is more reliable to estimate the shift of the septum pellucidum and third ventricle from the true anatomical cranial midline than to rely on measurements to the outer table of the skull. (R. M. S.)

Anoxemia and Early Activity in Fœtus.—The authors' experiments lend support for the view that more or less discrete movements in mammalian embryos are not the primary units but that these break off, as it were, from some sort of a mass movement that constitutes the basic pattern of behaviour. (R. M. S.)

Congenital Demyelinating Encephalopathy.—Three cases of a nonfamilial form of demyelinating encephalopathy are recorded, in each of which the origin was probably congenital. In two cases death occurred from intercurrent infection at the ages of two and three years, respectively, while in the third the patient died in her fifteenth year. All the patients had microcephaly, idiocy, convulsions, and cerebral spastic paralysis. Pathologically there were widespread demyelination and destruction of axis-cylinders and glia, without mesodermal infiltrations. In one case the disease was nonprogressive, and in all three the glial reaction was minimal. The best name for this condition seems to be congenital demyelinating encephalopathy. (R. M. S.)

Topographic Relations of Sleep-Regulating Centre.—Clinical and anatomical observations in two cases support the view that there is a definite region in the hypothalamus the intactness of which is essential in maintaining the more or less rhythmic alternation between the sleeping and the waking state. (R. M. S.)

Agenesis of Corpus Callosum.—The authors' case of total agenesis of the corpus callosum is the ninth in which this condition has been recognized during life and the second in which the diagnosis has been confirmed by both operative inspection and autopsy. (R. M. S.)

ARCHIVOS ARGENTINOS DE NEUROLOGIA

Vol. 21. Nos. 3–4. September–October 1939.

III Congreso Neurológico Internacional de Copenhague, 1939. (The International Neurological Congress at Copenhagen, 1939.) M. Balado. 81.

Nuevo Dispositivo Quirúrgico para la Neurocirugia. J. A. Ghersi. 253.

BRAIN

Vol. 62. No. 4. December 1939.

*Congenital Myotonia in the Goat. G. L. Brown and A. M. Harvey. 341.
*Observations on the Effects of Trigeminal Denervation. G. F. Rowbotham. 364.
*The Congenital Facial Diplegia Syndrome : Clinical Features, Pathology, and Ætiology. J. L. Henderson. 381.
*Dynamics of Homonymous Hemianopias and Preservation of Central Vision. M. B. Bender and M. G. Kanzer. 404.
*Blood Changes in Dystrophia Myotonica. J. N. Cumings and O. Maas. 422.
*A Biochemical Study of Cerebral Tissue, and of the Changes in Cerebral Œdema. A. M. Stewart-Wallace. 426.

Congenital Myotonia.—Myographic and electrical investigations of muscles from myotonic goats show a persistent irregular tetanus of muscle fibre groups which persists after nerve degeneration and curarization, but which is abolished by quinine. The response to a single nerve volley is repetitive and unusually great, and tetanic contraction persists after rapidly repeated nerve stimulation. The duration of contraction following acetyl choline is abnormally long and the muscle is hypersensitive to potassium. It is concluded that the abnormality is in the muscle itself, the neuro-muscular transmitting mechanism being normal. (D. J. W.)

Trigeminal Denervation.—Clinical testing of patients after surgical interference with the trigeminal nerve has confirmed that taste is only affected in so far as common sensation enters into the appreciation of taste, that the entire cornea is supplied by the first division, that proprioceptor fibres are carried from the tongue, and that the great superficial petrosal nerve contains palatal taste fibres and secretory nerves to the nose and eye. (D. J. W.)

Congenital Facial Diplegia.—A syndrome of congenital facial diplegia, ante-partum in origin, and often associated with partial or complete external ophthalmoplegia, ptosis, trigeminal and lingual palsy, club feet or other abnormalities, is described. It is due to non-development of the appropriate nuclei. (D. J. W.)

Dynamics of Homonymous Hemianopias.—Another explanation of macular sparing is based upon a conception of the functional unity of the optic radiation. It is supported by measurement of visual deterioration with progressive hemianopic defects. (D. J. W.)

Blood Changes in Dystrophia Myotonica.—There is fall in serum potassium during exercise in markedly myotonic subjects. This is probably due to excessive utilization by the abnormal muscles, which have a low K content at rest. (D. J. W.)

Cerebral Tissue and Changes in Cerebral Œdema.—The water and inorganic salt content of normal grey and white matter have been determined and compared. The increase of water content in cerebral œdema is confined to the white matter. The œdema results from a serum filtrate accumulating in the interstitial tissue, and it does not vary with the type of causal lesion. (D. J. W.)

CLINICAL SCIENCE

Vol. 4. No. 2. December 1939.

*Observations on the Oxygen Content of Venous Blood from the Arm Vein and on the Oxygen Consumption of Resting Human Muscle. H. E. Holling. 103.
Cure of Experimental Renal Hypertension. S. Cerqua and A. Samaan. 113.
Insulin-Sensitive and Insulin-Insensitive Types of Diabetes Mellitus. H. P. Himsworth and R. B. Kerr. 119.
Age and Insulin Sensitivity. H. P. Himsworth and R. B. Kerr. 153.
*The Fibre Dissociation produced by Cooling Human Nerves. R. G. Bickford. 159.
A Rapid Method of determining Lung Capacity. J. McMichael. 167.
Postural Changes in the Lung Volume. J. McMichael and J. P. McGibbon. 175.
The Effect of Œstrogens on the Urinary Creatinine of Castrate and Menopausal Women. E. P. Sharpey-Schafer and I. Schrire. 185.
Some Painful Joint Conditions and Their Relation to Osteoarthritis. J. H. Kellgren. 193.
Hypertension produced in the Rabbit by prolonged Renin Infusion. J. R. Hill and G. W. Pickering. 207.

Oxygen Content and Consumption.—In the muscles of the forearm the oxygen consumption is 0·07 c.c. per gm. per hour. Adrenaline in low concentration increases the blood flow without altering the oxygen consumption. (W. M. H.)

Fibre Dissociation by Cooling Human Nerves.—In man on cooling a nerve by an element at 15° C. there is first intense aching under the element and hyperalgesia in the nerve area, then loss of sensation of cold, motor and vasomotor paresis, loss of sensation of first pain, touch, second pain, and warmth in this order. (W. M. H.)

L'ENCÉPHALE

Vol. 34 (1). No. 5. May 1939.

La Thérapeutique Convulsivante par le Cardiazol en dehors de la Démence Précoce et des États Schizophréniques. (Cardiazol convulsive therapy in dementia præcox and schizophrenic states.) P. Delmas-Marsalet, M. Bergouignan, and J. Lafon. 225.

Contribution à l'Étude des Démences Préséniles. (Contribution to the study of presenile dementia.) H. Claude and J. Cuel. 243.

Sur la Forme Douloureuse de la Névrite Hypertrophique Familiale. (The painful form of familial hypertrophic neuritis.) S. Davidenkoff. 261.

Résultats de l'Insulinthérapie seule ou Associée à la Cardiazolthérapie et Conclusions Pratiques. (Results of insulin therapy, alone or associated with cardiazol therapy, and practical conclusions.) Leulier, Leclercq, Casalis, and Cappelle. 268.

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Vol. 39. No. 6. June 1939.

Second Dutch-Belgian Congress of Neurology and Psychiatry, Ghent and Brussels September 1938.

Les Rapports Cliniques entre les Encéphalites et la Démence Précoce. (Clinical relationship between encephalitis and dementia præcox.) Vermeylen. 389.

Indicaties bij de Toepassing der Individual-Psychologische Behandelingsmethodiek. E. A. D. E. Carp. 404.

Trois Cas d'Encéphalite avec Stase Papillaire. (Three cases of encephalitis with papilœdema.) Van Gehuchten. 407.

Un Cas de Démence Précoce Postencéphalitique. (A case of post-encephalitic dementia præcox.) J. Titeca. 417.

De Beteekenis van het Doodsbeleven bij Insuline en Cardiazol-Behandeling. A. H. Fortanier. 428.

Quelques Remarques sur la Névrose Obsessionelle du Point de Vue de la Psychanalyse. (Some remarks on obsessional neurosis from the point of view of psychoanalysis.) R. de Monchy. 433.

Over het Bloedeiwitspectrum en de Bezinkingssnelheid van de Erytrocyten bij Lijders aan Psychose. J. A. Ligterink. 437.

Le Problème des Plaques Séniles. (The problem of senile plaques.) P. Divry. 444.

Vol. 39. No. 7. June 1939.

Second Dutch-Belgian Congress of Neurology and Psychiatry, Ghent and Brussels September 1938—*continued.*

De Indivueele reactiewijwe bij Psychophysiologisch onderzoek. (Forms of individual reaction in the course of psychophysiological examinations.) B. Stokvis. 463.

Phénomène Nerveux au Cours de la Compression du Sinus Carotidien. (Nervous phenomena in the course of compression of the carotid sinus.) C. Heymans and J. J. Bouckaert. 469.

Idiotie avec Amaurose chez un Enfant d'Israélite Polonais en dehors de la Maladie de Tay-Sachs avec Projections). (Idiocy with amaurosis in the child of a Polish Jew, but not Tay-Sachs' disease.) L. van Bogaert. 471.

Proefondervindelijke vaststellingen betreffende de beteekenis van het plethysmographisch niveau. R. Nyssen and R. Busschaert. 473.

Considérations Psychologiques sur les Traitements avec l'Insuline et le Cardiazol. (Psychological aspect in treatment with insulin and cardiazol.) A. H. Fortanier. 483.

*L'Analyse Histo-Pathologique de la Maladie de Tay-Sachs. (Histopathological analysis of Tay-Sachs' disease.) C. Schaffer. 515.

*Tumeurs Métastatiques de la Fosse Postérieure chez les Malades ayant Atteint la Seconde Moitié de la Vie (Note Préliminaire). (Metastatic tumours of the posterior fossa in patients in the second half of life.) J. de Busscher. 534.

Histopathology of Tay-Sachs' Disease.—Schaffer describes the histological features in detail and emphasizes that the primary change is the degeneration of the hyaloplasm of the cells and that the depositon of prelipoid granules is purely secondary and not responsible for the swelling of the cells. He insists on the separate identities of pure cases of Tay-Sachs' and Niemann-Pick's disease. In the former the lecithin content of the brain is below normal, in the latter nearly twice normal ; in Niemann-Pick's disease the lecithin immigrates into the cells of the nervous system, whereas in Tay-Sachs' disease the prelipoid has a local origin. Tay-Sachs' is a disease of the extoderm, Niemann-Pick's one of the mesoderm. The foam cells of Pick are not found in Tay-Sachs' disease. (M. J. McA.)

Metastatic Tumour of Posterior Fossa.—Out of 32 cases with cerebral secondaries 17 showed deposits below the tentorium cerebelli. Thirteen of these 17 cases were over 45 years of age. As a cause of cerebellar tumour in a person in the second half of life secondary carcinoma must always be carefully considered. (M. J. McA.)

Vol. 39. No. 8. August 1939.

Second Dutch-Belgian Congress of Neurology and Psychiatry, Ghent and Brussels September 1938—*concluded.*

A Propos du Traitement des Affections Allergiques par le Pentaméthylènetétrazol. (The treatment of allergic diseases by pentamethylenetetrazol.) A. Leroy. 551.

De afferents en efferente verbindingen van de autonome hypothalamische centra en de vraag de ortho-en parasympathische functies in den hypothalamus. C. U. A. Kappers. 554.

*Organisation de Thalamus et du Cortex Cérébral chez le Lapin. (The nature of the thalamus and cerebral cortex in the rabbit.) J. Stoffels. 557.

Kyste dermoïde de la Queue de Cheval dans un Cas de Rachischisis. (Dermoid cyst of the cauda equina in a case of spina bifida.) H. de Jong. 576.

Filmdemonstratie : Catatonie bij mensch en dier. J. de Jong. 578.

A Propos du Diagnostic et Traitement Chirurgical des Anomalies Congénitales du Système Nerveux et de ses Méninges. (The diagnosis and surgical treatment of congenital anomalies of the nervous system and its meninges.) A. Oljenick. 579.

De Neuro-Chirurgie der Hersenzenuwen. F. A. L. J. Verbeeck. 580.

Over hyperostosis frontalis interna en aanverwante syndromen. G. Muyle. 580.

Chondrome s'Etant Substitué à presque tout l'Hémisphère Cérébral Gauche d'un Enfant de 13 Ans. J. de Busscher. 580.

Lobair-Atrophie van Pick. (Pick's disease.) V. W. D. Schenk. 581.

*Les Formes de Croissance des Gliomas et leur Importance Pratique. (Forms of growth in the gliomas and their practical importance.) H. J. Scherer. 591.

Les Voies Centrales de la Sensibilité. (Note Preliminaire.) (The central pathways of sensation.) M. A. Gerebzoff. 598.

Thalamus and Cerebral Cortex in Rabbit.—An experimental anatomical study of the thalamo-cortical projections, the systematization of the thalamic and cortical topography, and the rôle of the various groups of thalamic ganglia. (M. J. McA.)

Modes of Growth and Extension of Gliomas.—Scherer has studied in detail 106 cases of gliomas. He stresses the fact that microscopically gliomas are almost always much more extensive than would seem from the naked eye. Multicentric gliomas (more than 10 per cent.) and diffuse gliomas (about 65 per cent.) are more frequent than those relatively circumscribed (about 25 per cent.); the latter are mainly oligodendrogliomas and small-celled glioblastomas. Cerebral astrocytomas are always diffuse, extensive, and infiltrating. Certain secondary factors may limit the growth of gliomas which are histologically very malignant, such as a process of cicatrization round a necrotic zone occupying the greater part of a tumour, degenerative processes at the edge of the tumour, a sharp arrest of the tumour at certain anatomical boundaries such as the cerebral cortex, etc. However, these factors never influence the growth of an astrocytoma, which is always diffuse and does not show necrosis or cicatrization. Certain tumours which spring from the hippocampus or septum pellucidum develop almost entirely in the ventricular cavity and are scarcely infiltrating. The only glioma which grows solely by pushing back other structures is the ependymoma; all the others are in principal infiltrating. Thirty per cent. of gliomas are bilateral and almost all the gliomas of the thalamus or hypothalamus, apparently unilateral, are microscopically bilateral. (M. J. McA.)

Vol. 39. No. 9. September 1939.

*L'Azoman dans la Thérapeutique de la Schizophrenie. (Azoman in the treatment of schizophrenia.) H. Hoven. 607.

Psychose de Korsakow avec Polynévrite au Cours d'une Septicémie Post-Puerpérale. (Korsakow's syndrome with polyneuritis during the course of post-puerperal septicæmia.) M. Maere. 616.

*Méningite à Pneumocoque Guérie par la Sulfamidothérapie. (Pneumococcal meningitis cured by sulphanilamide. E. Evrard and A. Bragard. 622.

Azoman and Schizophrenia.—Hoven reports favourably on convulsion therapy with Azoman (triazol 156) in schizophrenia. He stresses its advantages over cardiazol and usually gives it intramuscularly. Fractures are less common. Out of 120 cases treated 50 made a complete or social cure and the majority had been ill 2–5 years. Combined with insulin he regards it as the treatment of choice in long-standing cases. (M. J. McA.)

Meningitis and Sulphanilamide.—The authors advise the following dosage of dagenan 693 in suppurative meningitis: 6–8 gm. the first day, 6 gm. daily for the next 2–4 days, and then gradual reduction, it being prudent to continue the drug for 10 days after disappearance of signs of meningitis in the c.s.f. Oral administration is usually adequate, except sometimes at the onset of treatment. Intrathecal administration is very rarely needed and has dangers. Early intensive treatment is essential. (M. J. McA.)

Vol. 39. No. 10. October 1939.

Un Méningiome de l'Olfactif. (An olfactory meningioma.) J. Helsmoortel and H. J. Scherer. 647.

Myoclonies Rythmiques du Voile et du Larynx chez un Sujet Jeune ne Présentant, en dehors de Signes Névropathiques, qu'une Dissociation Albumino Citologique du Liquide. (Rhythmic myoclonus of palate and larynx in a young subject who, beyond neuropathic signs, showed only an albumino-cytological dissociation in the c.s.f. Discussion

of myoclonus seen in conditions thought to be functional.) J. Rademecker and J. Helsmoortel. 654.

Hérédo-Ataxie Cérébelleuse de P. Marie. (Marie's heredo-cerebellar ataxia.) V. Gallemaerts, F. Kleyntjens, and W. Cloetens. 667.

Influence de l'Extrait Pancréatique Désinsuliné sur Certains Etats Épileptiques. (Influence of deinsulinized pancreatic extract on certain epileptic states.) C. Rouvroy. 676.

Paranoïa et Homosexualité. (Paranoia and homosexuality.) J. de Busscher. 691.

Vol. 39. No. 11. November 1939.

Sur les Cavités Kystiques des Néoplasmes Cérébraux Rendues Visibles par Injection de Thorotrast. (Cystic cavities in cerebral neoplasms made apparent by injection of thorotrast.) T. Lehoczky. 715.

Contribution à l'Étude des Voies Afférentes de l'Olive Inférieure. (Contribution to the study of the afferent pathways of the inferior olive.) M. A. Gerebtzoff. 719.

Polynévrite Toxique Provoquée par l'Ulirone. (Toxic polyneuritis induced by Urilone.) A. Leroy. 729.

Traitement de la Migraine par les Injections Intramusculaires de Pentaméthylènetétrazol. (Treatment of migraine by intramuscular injections of cardiazol.) 735.

La Projection des Noyaux Antérieurs du Thalamus sur l'Écorce Interhémisphérique (Première partie). (The projection of the anterior nuclei of the thalamus on the interhemispherical cortex in the rabbit (1st part).) J. Stoffels. 743.

JOURNAL OF CLINICAL INVESTIGATION

Vol. 19. No. 1. January 1940.

Serum Phosphatase in the Lymphomatoid Diseases. H. Q. Woodard and L. F. Craver. 1.

Precipitin Studies in Nephrosis and Nephritis. E. Goettsch and J. D. Lyttle. 9.

*Nature of Peripheral Resistance in Arterial Hypertension. E. A. Stead and P. Kunkel. 25.

The Circulation in Athletes. H. J. Stewart and R. F. Watson. 35.

Serum Lipoids and Proteins in Hyperthyroidism. E. B. Man, E. F. Gildea, and J. P. Peters. 43.

The Decrease of Gastric Secretion with Advancing Years: Further Observations. A. L. Bloomfield. 61.

The Streptococcal Antifibrinolysin Test in Clinical Use. P. L. Boisvert. 65.

The Antistreptolysin Titer in Rheumatic Fever, Arthritis, and Other Diseases. J. J. Bunim and C. McEwen. 65.

The Relation of Methemoglobin to the Cyanosis observed after Sulfanilamide Administration. I. Vigness, C. J. Watson, and W. W. Spink. 83.

The Renal Excretion of Inulin at Low Plasma Concentrations of This Compound, and Its Relationship to the Glomerular Filtration Rate in Normal, Nephritic, and Hypertensive Individuals. B. F. Miller, A. S. Alving, and J. Rubin. 89.

The Control of the Dosage of Antiserum in the Treatment of Pneumococcal Pneumonia:
I. A Study of the Mechanism of the Skin Reaction to Type Specific Polysaccharide. W. B. Wood. 95.
II. The Clinical Application of the Francis Skin Test. W. B. Wood. 105.

The Occurrence of Methemoglobinemia during Sulfanilamide Therapy. C. L. Fox and J. E. Cline. 123.

Effect of Disease of the Liver and Biliary Tract upon the Phosphatase Activity of the Serum. A. B. Gutman, K. B. Olson, E. B. Gutman, and C. A. Flood. 129.

Metabolic Disturbances in Experimental Human Vitamin B Deficiency. K. O'Shea Elsom, F. D. W. Lukens, E. H. Montgomery, and L. Jonas. 153.

Studies on the Action of Sulfapyridine on Pneumococci. W. C. Spring, F. C. Lowell, and M. Finland. 163.

Immunological Studies on Patients with Pneumococcal Pneumonia treated with Sulfapyridine. M. Finland, W. C. Spring, and F. C. Lowell. 179.

A Comparative Study of the Blood Concentrations and Urinary Excretion of Sulfapyridine and Sulfanilamide after Single Doses of Sulfapyridine and Related Compounds administered by Various Routes. F. H. L. Taylor, F. C. Lowell, M. A. Adams, W. C. Spring, and M. Finland. 201.

Bactericidal Action of Sodium Sulfapyridine and of a Glucose-sulfapyridine Solution in Human Blood. F. C. Lowell, W. C. Spring, and M. Finland. 215.

The Diodrast Clearance and Renal Blood Flow in Toxemias of Pregnancy. L. C. Chesley, M. J. Connell, E. R. Chesley, J. D. Katz, and C. S. Glissen. 219.

Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia. VIII. Further Studies of the Proteolytic Activity of Normal Human Gastric Juice *in Vitro*; and the Limitations of the Method in Pernicious Anemia. C. J. Gessler, S. O. Dexter, M. A. Adams, and F. H. L. Taylor. 225.

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Immunity in Diabetes. III. Relation of Tissue Glycogen and Blood Chemistry to Bacterial Dissemination, Antibody Formation, and Survival after Infection in Diabetes. R. Richardson. 239.

The Urinary Excretion in Riboflavin. Fluorometric Methods for Its Estimation. J. W. Ferrebee. 251.

Sulfapyridine in Experimental Pneumococcic Pneumonia in the Dog. L. A. Gregg, M. Hamburger, and C. G. Loosli. 257.

Peripheral Resistance in Hypertension.—The increased peripheral resistance present in arterial hypertension cannot be reduced to the normal level by powerful vasodilating stimuli. No evidence was found for a neurogenic origin for the hypertension. Permanent vascular damage takes place after original active vasoconstriction has occurred. (J. N. C.)

JOURNAL OF COMPARATIVE NEUROLOGY

Vol. 71. No. 1. September 1939.

The Capillary Beds of the Paraventricular and Supraoptic Nuclei of the Hypothalamus. K. H. Finley. 1.

The Hypoglossal Nerve in Human Embryos. A. A. Pearson. 21.

Motor Seizures accompanying Small Cerebellar Lesions in Cats. S. L. Clark. 41.

The Origin, Course, and Terminations of the Secondary Pathways of the Trigeminal Nerve in Primates. A. E. Walker. 59.

Melanin Pigmentation of the Substantia Nigra in Primates. H. J. Scherer. 91.
The Pretectal Region of the Turtle, *Pseudemys scripta Troostii*. A. O. Curwen and R. N. Miller. 99.
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Certain Phylogenetic Anatomical Relations of Localizing Significance for the Mammalian Central Nervous System. R. T. Woodhouse. 215.
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Histogenesis of the Monopolar Neuroblast and the Ventral Longitudinal Path in the Albino Rat. A. W. Angulo y Gonzalez. 325.
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The Behaviour of the Neural Crest in the Forebrain Region of Amblystoma. R. C. Baker and G. O. Graves. 389.

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The Relative Vascularity of Subcortical Ganglia of the Cat's Brain ; the Putamen, Globus Pallidus, Substantia Nigra, Red Nucleus, and Geniculate Bodies. H. B. Hough and H. G. Wolff. 427.
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Cerebral Fiber Tracts of Amblystoma Tigrinum in Midlarval Stages. C. J. Herrick. 511.
The Telencephalon of Tubinambis Nigropunctatus. III. Amygdala. A. O. Curwen. 613.
Axon Hillocks of Multipolar Neurons of the Cat. Q. B. DeMarsh. 637.

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A Review of Gestalt Psychology. J. M. Blackburn. 1.
A Clinical Study of the Mescaline Psychosis, with Special Reference to the Mechanism of the Genesis of Schizophrenia and other Psychotic States. G. Tayleur Stockings. 29.
A Comparison between Some of the Effects of Isomyn (Benzedrine) and of Methylisomy. F. L. Golla, J. M. Blackburn, and S. Graham. 48.
A Rehabilitation and Resocialization Scheme for Psychopathic Patients. L. H. Wootton. 60.
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Lesions of the Spinal Column resulting from Convulsion Therapy. G. Kraus and H. J. Viersma. 76.
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Some Further Observations on Vitamin C Estimation in Psychotic and Psychopathic Patients. L. Minski and N. D. Constantine. 109.
" Stationary " General Paralysis of the Insane. A Report of a Case of Thirty-One Years' Duration. A. J. Galbraith. 112.

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Anomalous Cardiac Occurrences during Cardiazol Treatment of the Psychoses and Psychoneuroses. R. Good. 260.
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Observations on the Behaviour of Schizophrenic Patients undergoing Insulin Shock Therapy. C. Wall. 1.
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The Clinic and Pathology of Neurobrucellosis. E. M. Steblov. 4.
On Some Modifications of the Classical Method of Insulintherapy. M. I. Serejsky and N. N. Zak. 15.
The Histopathology of Hepato-Lenticular Degeneration. I. The Origin of Alzheimer's Glia. N. V. Konolavov. 18.
The Bioelectrical Function of the Brain in some Forms of Epilepsy. A. S. Penzik. 35.
The Djackson's Concept of the Pathology of the Brain. Z. L. Lurie. 46.
Some Experience in Stopping a Psychomotor Excitation by Administration of a Mixture of Bromide-Medinal-Magnesium. M. M. Klipzan. 52.

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Late Modifications of the Brain in Poisoning with Hydrocyanic Acid and Its Salts. P. E. Snessarev. 3.
Tumours of the Lobe of the Forehead. III. Differential Diagnosis. L. A. Shenderov. 17.
Myastenolepsy as Isolated Syndrom of the Narcolepsy (to the Clinic of Vegetomotor Syndrom). A. L. Nemlikher and P. I. Tseranskaya. 35.
To the Pathomorphology of the Nodes of the Marginal Trunk in Hyperergic Inflammation (Schwarzmann's Phenomenon). An Experimental Investigation. B. G. Rubinstein and A. S. Livshin. 48.
Some Peculiarities of the Defect after a Range of Endured Acute Outbreaks of Schizophrenia and the Influence of the Postacute Protracted Conditions on the Course of the Process. A. R. Gourvich. 54.
Blood Transfusion in the Therapeutics of Mental Diseases. G. J. Malis. 63.
An Essay of the Work with Logoneurotics of Preschool Age. N. A. Vlasovs and E. N. Herzensten. 68.
Rhythmics with Logoneurotics of Preschool Age. N. R. Samoilenko. 77.

JOURNAL OF NEUROPHYSIOLOGY

Vol. 2. No. 6. November 1939.

*Physiological Analysis of the General Cortex in Reptiles and Birds. F. Bremer, R. S. Dow, and G. Moruzzi. 473.
Studies in the Physiology of the Embryonic Nervous System : IV. Development of Acetylcholine in the Chick Embryo. Z. Y. Kuo. 488.
Effects of Acoustic Stimuli on the Waking Human Brain. P. A. Davis. 494.
Electrical Reactions of the Human Brain to Auditory Stimulation during Sleep. H. Davis, P. A. Davis, A. L. Loomis, E. N. Harvey, and G. Hobart. 500.
Conditioning of Afferent Impulses by Reflex Discharges over the Dorsal Roots. J. F. Toennies. 515.
Spinal Pathways for Nictitating Membrane Reflexes in the Cat. S. H. Armstrong and D. McK. Rioch. 526.
Vagal Inhibition of Inspiration, and Accompanying Changes of Respiratory Rhythm. T. E. Boyd and C. A. Maaske. 533.
*Cerebellar Action Potentials in Response to Stimulation of Various Afferent Connections. R. S. Dow. 543.
*Changes in Retinal Excitability due to Polarization and Some Observations on the Relation between the Processes in Retina and Nerve. R. Granit and T. Helme. 556.
The Effect of Eserine on Spinal Reflexes in the Dog. J. K. Merlis and H. Lawson. 566.

General Cortex in Reptiles and Birds.—The cerebral cortex of the turtle is electrically unexcitable ; that of the pigeon excitable by a weak current, deviation of the head and eyes occurring on unilateral stimulation and pecking movements on simultaneous bilateral excitation. Since the spontaneous electrical activity of the cortex of the unanæsthetized pigeon is not wholly removed on superficial cocainization, it must have subcortical component. The cerebral cortex of the pigeon gives a large initial wave on illumination of contralateral eye. (W. M. H.)

Cerebellar Action Potentials.—An oscillographic study which expands anatomic evidence of the cerebellar afferents. Stimulation of the 8th nerve gives electrical responses in the flocculo-nodular lobe, lingula, uvula, and the fastigial nucleus ; stimulation of the spinal nerves responses in anterior lobe, pyramis, lobulus simplex. Stimulation in the region of the inferior olivary nuclei causes transynaptically potentials in all the lobes. With different afferents dissimilar potentials may arise at the same point. (W. M. H.)

Retinal Excitability and Polarization.—when a galvanic current crosses the retina, the cathode being within the bulb, the electroretinogram and the discharge in the optic nerve are enhanced. The "off discharge" in the nerve is preceded by a small initial retinal positivity. The main part of the retinal off effect follows the discharge in the nerve. (W. M. H.)

JOURNAL OF PHYSIOLOGY

Vol. 97. No. 2. December 1939.

The Air Stream in the Lung of the Fowl. J. D. P. Graham. 133.
Vaginal Potentials in Rabbits. R. B. Bourdillon. 138.
*Impulses in the Pyramidal Tract. E. D. Adrian and G. Moruzzi. 153.
The Effect of Anterior Pituitary Extracts on the

Insulin Content of the Pancreas. C. H. Best, J. Campbell, and R. E. Haist. 200.
*Afferent Impulses from the Teeth due to Pressure and Noxious Stimulation. C. Pfaffmann. 207.
*Afferent Impulses from the Teeth resulting from a Vibratory Stimulus. C. Pfaffmann. 220.
The Diffusion of Chloride and Glucose into Frog Muscle. R. B. Fisher and V. Subrahmanyan. 233.
Fatty Infiltration of the Liver in Pregnant Ewes. L. C. Snook. 238.
Vascular Changes affecting the Transmission of Nervous Impulses. E. Bülbring and J. H. Burn. 250.
*Amine Oxidase and Adrenaline. D. Richter and A. H. Tingey. 265.

Impulses in Pyramidal Tract.—Too lengthy adequately to summarize. Pyramidal fibre discharges are compared with potential waves in the motor area and conditions of Betz cell activity in anæsthesia following sensory stimulation and convulsive drugs are described. (W. M. H.)

Afferent Impulses from Teeth due to Pressure.—Most of the endings responsible for nerve discharges evoked by touch and pressure lie in the periodontal membrane. Endings for pressure vary considerably in their adaptation times; for the single ending pressure rather than tension is the adequate stimulus; the frequency of discharge is influenced by the rate of application and the final pressure applied. Touch endings in the tongue mucous membrane respond to changes in pressure but not to steady deformation. Their threshold is lower than that of the pressure endings. Noxious agents on the tooth give impulses of lower voltage and conduction rate than those evoked by pressure on the intact tooth. (W. M. H.)

Afferent Impulses from Teeth with Vibratory Stimulus.—The oscillatory discharge in the dental nerve follows up to 1,500 cycles the frequency of a vibrating stylus applied to the tooth. The highest frequency of "following" in single fibres is 900–1,000 cycles. Different endings have different maximal frequencies of response, related to other properties of the ending, e.g. maximal frequency of response to rapid pressure change and adaptation time. Endings may be activated at frequencies overlapping the relative refractory period of the nerve. (W. M. H.)

Amine Oxidase and Adrenaline.—With 10^{-7} adrenaline as substrate, 10^{-3} ephedrine inhibited oxidation by amine oxidase by only 50 per cent. From the rate it inactivates adrenaline in concentrations down to 10^{-1} and from its concentration in the liver, amine oxidase would not appear to be specifically concerned in the inactivation of sympathin or adrenalin. (W. M. H.)

Vol. 97. No. 3. January 1940.

*Vascular Reactions of the Cat after Total Sympathectomy. G. L. Brown and W. d'A. Maycock. 273.
The Sympathomimetic Action of Local Anæsthetics. J. Tripod. 289.
The Inhibition of Adrenaline Oxidation by Local Anæsthetics. F. J. Philpot. 301.
On the Primary Acidity of the Gastric Juice. T. Teorell. 308.
The Action in the Perfused Liver of Acetylcholine, Sympathomimetic Substances, and Local Anæsthetics. M. Chakravarti and J. Tripod. 316.
*Effects of Changes in Dietary Calcium on Neuromuscular Transmission. G. L. Brown and A. M. Harvey. 330.
*The Oxygen Supply of the Fœtal Brain of the Sheep and the Effect of Asphyxia on Fœtal Respiratory Movement. J. Barcroft, D. H. Barron, A. T. Cowie, and P. H. Forsham. 338.
Oxygen in the Blood of the Umbilical Vessels of the Sheep. J. Barcroft, J. A. Kennedy, and M. F. Mason. 347.
Effect of Acetylcholine, Prostigmine, Potassium, and Fatigue on the Crossed Extensor Reflex and on Its Reflex Inhibition in the Toad. C. Torda. 357.
The Influence of Diuretics on the Osmotic Work done and on the Efficiency of the Isolated Kidney of the Dog. M. G. Eggleton, J. R. Pappenheimer, and F. R. Winton. 363.
The Production of Exophthalmos in the Dog by Acetylcholine. C. E. Brunton. 383.
Effects of Increased Metabolism on Ketosis of Depancreatized Dogs. S. B. Barker. 394.
*Calcium and Synaptic Transmission in a Sympathetic Ganglion. A. M. Harvey and F. C. McIntosh. 408.
On the Disappearance from the Blood of Intravenously Injected Insulin. H. G. Goadby and J. S. Richardson. 417.
A Circulation Model. L. E. Bayliss. 429.

Vascular Reactions after Sympathectomy.—Curarine abolished the fall in blood pressure, evoked by stimulation of sensory nerves or anterior roots in the sympathectomized cat; but it fails to prevent the fall which follows manipulation or transection of the spinal cord when the blood pressure is high. This suggests a vasoconstrictor pathway other than the thoraco-lumbar outflow. (W. M. H.)

Calcium and Neuromuscular Transmission.—Neuromuscular transmission was examined in a kid kept on a diet deficient in calcium. A single maximal motor nerve volley failed to produce a maximal response from the muscle. With stimulation at a high frequency the successive responses of the muscles became greater till transmission was full at the 5th or 6th response. This defect is similar to that normally seen in the fowl. (W. M. H.)

Oxygen Supply of Fœtal Brain.—In the fœtal sheep the oxygen saturation of the carotid blood is comparable to that in arteries of persons at high altitudes. In the week before birth it falls markedly. The oxygen in the blood of the venous sinuses of the brain gives an index of the degree of asphyxia necessary to produce

respiratory movements by release of the inhibitory centre in the forebrain. (W. M. H.)

- **Calcium and Synaptic Transmission.**—In the absence of calcium ions the sympathetic ganglion discharges impulses spontaneously and fails to transmit preganglionic impulses. There is a failure in output of acetyl choline evoked by preganglionic stimulation or by potassium ions. The ganglion cells are sensitized to both the stimulating and paralysing actions of injected potassium chloride. (W. M. H.)

PHYSIOLOGICAL REVIEWS

Vol. 20. No. 1. January 1940.

Chemical Changes in the Blood and Their Clinical Significance. V. C. Myers and E. Muntwyler. 1.
Metallic Elements and Blood Formation. M. O. Schultze. 37.
Immunity in Invertebrates. C. G. Huff. 68.
The Functional Significance of Specific Agglutinins and Precipitins. P. R. Cannon. 89.
Functions of the Carotid and Aortic Bodies. C. F. Schmidt and J. H. Comroe. 115.

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Vol. 14. No. 1. January 1940.

Freud—The Man. C. P. McCord. 3.
Sexual Manifestations in Neurotic and Psychotic Symptoms. A. A. Brill. 9.
Clinicopathologic Study of a Case of Pick's Disease. A. Ferraro and G. A. Jervis. 17.
Suicide as Wish-fulfilment. I. Hendrick. 30.
Effect of Metrazol Injections on the Electroencephalogram. H. Strauss and W. E. Rahm. 43.
Psychopathic States with Psychotic Reactions. J. L. Nelson and J. Zimmerman. 49.
Six Cases of Psychosis associated with Illuminating Gas Poisoning. A. G. Rodgers. 61.
Combined Insulin and Metrazol in the Treatment of Psychoses. S. J. Tillim. 81.
Prepsychotic Personality in Alcoholic Psychoses. E. Davidoff and C. A. Whitaker. 103.
The Aggravation of Mental Symptoms by Excessive Use of Hypnotics and Sedatives. L. S. Wondolowski. 121.
Injuries sustained during the Course of Metrazol Shock Therapy. C. C. Graves and F. P. Pignataro. 128.
Malaria Therapy for the Nonhospitalized Case of Neurosyphilis. W. A. Thompson. 135.
Schizophrenic "Deterioration." S. R. Lehrman. 140.
Folliculin Menformon (Theelin) Treatment of Involutional Melancholia. J. Notkin, B. Dennes, and V. Huddart. 157.
Involutional Melancholia. C. L. Wittson. 167.
Five Years' Work with Cerebral Palsy. J. Sirkin. 185.
Acute Heterosexual Inadequacy. J. E. Oltman and S. Friendman. 194.

RIVISTA DI NEUROLOGIA (NAPOLI)

Vol. 12. No. 6. December 1939.

*Provocazione di Accessi Convulsivi nel Coniglio Mediante la Iniezione Endocisternale di Soluzioni Inorganiche. (The provocation of convulsive attacks in rabbits by the injection into the cisterna of inorganic solutions.) G. Glück. 389.
*Contributo alla Cura Chirurgica della Paralisi Traumatica del Nervo Radiale nelle Fratture Chiuse della Diafisi dell'Omero. (A contribution to the surgical treatment of traumatic paralysis of the radial nerve in simple fracture of the shaft of the humerus.) E. Repetto. 400.
*Sulla Reazione di Rosegger nel Liquido Cefalo-Rachidiano. (On the reaction of Rosegger in the cerebrospinal fluid.) S. Tolone and V. Janson. 414.
La Nevralgia del Glossofaringeo e le Nevrialgie Auricolofacciali. (Glossopharyngeal neuralgia and auriculo facial neuralgias.) C. Pero. 433.

Convulsions in Rabbits by Injection.—While the alkalinity of the substance injected favours convulsive reaction the chemical composition and concentration is even more important, the most marked results being obtained by 1 per cent. sodium carbonate, 2 per cent. potassium carbonate, and saturated solution of lithium carbonate. The author warns the reader against drawing conclusions relative to human epilepsy from experimental results. (R. G. G.)

Surgical Treatment of Radial Nerve Paralysis.—Two cases are described. The nerve trunk is not divided, but becomes involved in callous and scar tissue. This nerve trunk must be freed and transplanted so that it cannot again become so involved. The author thinks that surgical intervention is always necessary in such cases and is the only method of securing good results and complete cure. (R. G. G.)

Rosegger's Reaction in C.S.F.—This reaction of protein precipitation is very sensitive, but not practically very useful, since it does not distinguish between meningeal and neuroluetic processes. The reaction is due to a variety of physicochemical changes which may be produced by a variety of morbid conditions and this accounts for its lack of specificity. (R. G. G.)

RIVISTA DI PATOLOGIA NERVOSA E MENTALE

Vol. 54. No. 1. July–August 1939.

*Istopatologia della Malattia di Schilder Familiare. (Histopathology of familial Schilder's disease.) F. Cardona. 1.

La Struttura dell'Epiphysis Cerebri in Rapporto alla Castrazione ed alla Gravidanza. (The structures of the cerebral epiphysis in relation to castration and pregnancy.) G. Godina. 74.

*Su una Rara Sindrome Clonica degli Occhi e dei Muscoli Scheletrici (oftalmo-mio-clonia) in un Caso di Atassia Cerebellare Acuta. (On a rare syndrome showing clonus of the eyes and of the skeletal muscles (ophthalmo-myo-clonia) in a case of acute cerebellar ataxia.) O. Mallaguzzi-Valeri. 103.

Errori, Dubbi e Certezze Riguardo alle Variazioni della Pressione Rachidea dopo Puntura Lombare. (Errors, doubtful and certain, with regard to the variations of fluid pressure after lumbar puncture.) A. Pacifico. 131.

*I Quadri Clinici della (Regressio Mentis Infanto-Juvenilis). (The clinical picture of infanto-juvenile mental regression.) A. Paleari. 139.

*Richerche Sperimentali sulla Considdetta Degenerazione Transneuronica. (Experimental research on the so-called transneuronic degeneration.) R. Angelico. 161.

Histopathology of Schilder's Disease.—The author has studied from the histopathological point of view the brain of two brothers who died at a short interval of time from a diffuse demyelinization of the white matter, especially in the centrum ovale. He discusses the symptoms of the anatomical syndrome and the ideas of various authors on the demyelinating diseases. In the cases described the process was degenerative and there were indications of a diffuse alteration in the lipoid metabolism throughout the neuraxis. The author does not believe in the theory that Schilder's disease depends on a generalized dysfunction of the glia or that the chief alteration is in the oligodendroglial mucosa. Nor does he agree that all cases of Schilder's disease are of the same type, but thinks that there is one group of toxic-inflammatory cases and another of degenerative cases which are mostly familial and which depend on alterations in the lipoid metabolism and have points of contact with so-called lipoidosis. (R. G. G.)

Clonus of Eyes and Skeletal Muscles in Cerebellar Ataxia.—This syndrome, together with muscular hypotonia and signs of cerebellar ataxia and astasia, were observed to occur in a child the subject of a moderately severe infectious illness. Rare analogous cases have been described by Polish authors resulting from lesions in the vermis and nuclei dentata, and the author thinks that the localization of the lesion was similar in his case. He suggests that the virus of poliomyelitis may have been responsible. (R. G. G.)

Infanto-Juvenile Mental Regression.—The author discusses the various forms of this mental deterioration in early childhood and does not consider that endocrine treatment, pyrotherapy, or convulsive therapy hold out much hope, but thinks that in the milder cases patient and well-planned re-education may be worth trying. (R. G. G.)

Transneuronic Degeneration. — Experimental lesions of the superior cerebellar peduncle resulted in alterations in the cellular elements of the opposite red nucleus. These alterations were found in the nigroid substance, the cells showing central or peripheral chromatolysis, with changes in the nuclei. Since there is no direct neural connection between the two areas the changes which were transitory must have been due to the suppression of customary stimuli. It is therefore necessary to separate the concept of transneuronic reaction or irritation from that of degeneration. (R. G. G.)

Vol. 54. No. 2. September–October 1939.

*Contributo allo Studio dei Rapporti fra Paralisi Generale Progressiva e Senilita. (A contribution to the study of the relationship between paralysis and senility.) G. Gastaldi. 177.

Paralisi Ascendente di Landry. (Landry's ascending paralysis.) S. Platania. 237.

L'Influenza dell'Apparato Vestibolare sulle Percezioni Visive. (The influence of the vestibular apparatus on visual perception.) L. Longhi. 291.

*Metodo Rapido di Impregnazione della Nevroglia. (A rapid method for the impregnation of neuroglia.) R. Bozzi. 343.

Relationship between General Paralysis and Senility.—The author on the basis of ten personally observed cases, examines the clinical problem of general paralysis in patients of advanced age. He emphasizes the peculiarities of the incubation period, especially with regard to Meggendorfer's law; the possible influence of senile dementia on the neurosyphilitic process; and above all the distinction between the slow progressive paralysis and the course of senile dementia. The latter he shows to be worthy of recognition, at least within certain limits. Dealing with the morbid anatomy and pathology of the two processes, the author makes certain reservations with regard to Jakob's principle of inhibition, and goes on to illustrate a process of fibrosis associated with hypertrophy of the glia which he has observed in one of the cases examined. (R. G. G.)

Method for Impregnation of Neuroglia.—A method for the impregnation of the neuroglia with silver salts is described which reduces the time previously necessary for this process. It is, however, only effective when dealing with the white matter, since the neuroglia of the grey matter does not respond in every case. (R. G. G.)

Vol. 54. No. 3. November–December 1939.

*Sull'Avvelenamento Cerebrale Cronico da Manganese. (Chronic cerebral poisoning by manganese.) L. de Lisi. 349.
Rilievi Cronassimetrici in due Ammalati di Pellagra. (Chronaxial findings in two cases of pellagra.) I. Iavicoli. 388.
Sul Comportamento della Barriera Emato-Liquorale nei Pellagrosi. (On the behaviour of the barrier between blood and cerebrospinal fluid in cases of pellagra.) C. Trabucchi and G. Ferrari. 415.
Orientamenti Clinici e Nosografici dopo un Anno di Terapia Insulinica e Cardiazolica in Malati di Mente nella R. Clinica di San Salvi. (A clinical and symptomatic review of results after a year of treatment of mental diseases by insulin and cardiazol in the Royal Clinic of San Salvi.) C. E. Roberti. 425.
*Studi sui Fenomeni di Permeabilita del Tessuto Nervoso. I. La diffusione delle Sostanze Coloranti nel Parenchima Nervoso dell'Animale Morto. (Studies of the phenomena of diffusion in the central nervous system. I. Diffusion of colouring Matter in the nervous parenchyma of dead animals.) P. Sandri. 440.
*Studi sui Fenomeni di Permeabilita del Tessuto Nervoso. II. Influenza dell'Acidificazione sulla Diffusione delle Sostanze Coloranti nel Parenchima Nervoso. (Studies of the phenomena of diffusion in the central nervous system. II. Influence of acid fixation on the diffusion of the colouring matter in the nervous parenchyma.) P. Sandri. 451.
Sul Rigofiamento Acuto dell'Oligodendroglia nelle Psicosi Acute. (Acute swelling of the oligodendroglia in acute psychoses.) A. Campana. 461.

Cerebral Poisoning by Manganese.—A review of the general opinions on manganese poisoning is presented. The author describes the case of a 25-year-old youth who had shown symptoms of cerebral manganese poisoning from the end of his 15th year after having worked for a year in a wire factory. The author describes his own case and those recorded in the literature, and shows the difference between manganese poisoning and all the other extrapyramidal syndromes, including Wilson's disease, Parkinson's disease, and the Parkinsonianism of encephalitis. He concludes that chronic manganese poisoning shows a special characteristically complex picture involving both brain and spinal cord which may be included in the extrapyramidal group of syndromes, but more on the basis of a wide physio-pathological conception than on a restricted anatomo-clinical basis, which is now shown to be an entirely insufficient description. (R. G. G.)

Phenomena of Diffusion in C.N.S.—In an attempt to review critically certain ideas on the permeability of the blood-neuraxial barrier, experiments were made with various acid and basic colouring matter on diffusion into the brain of a dead dog. It was found that the depth of penetration in most cases correlated with the degree of dispersion of the solution of colouring matter. (R. G. G.)

Phenomena of Diffusion in C.N.S. (II).—Fragments of dogs brain of varying *p*H value were used *in vitro* for these experiments. It was found that acidification delayed diffusion of acid colouring substances and increased the rate of basic colours. This may be due to an alteration in molecular distribution or in electric tension in the colouring material or in the tissues. (R. G. G.)

SCHWEIZER ARCHIV FÜR NEUROLOGIE UND PSYCHIATRIE

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Zur pathologischen Anatomie der Epilepsie. (The pathological anatomy of epilepsy.) S. Baumatz. 209.
*Betrachtung über die Psychodynamik zwangsneurotischer Störungen in einem Fall mit manisch-depressiven Zuständen. (Observations on the psychodynamics of compulsion-neurotic disturbances in a case with manic-depressive features.) J. Flescher. 229.
*Zur Physiopathologie und Klinik des Nasenrückenlidreflexes. (Physiological and clinical investigation on bridge of nose–eyelid reflex.) A. Glattauer. 243.
*Les Tumeurs du Troisième Ventricule. (Tumours of the third ventricle.) A. Jentzer. 256.
*Vergiftungen durch chlorierte Kohlenwasserstoffe. (Poisoning with chlorine-carbon compounds.) R. Isenschmid. 288.
Die diagnostische Bedeutung des opkinetischen Nachnystagmus bei Commotio cerebri und anderen diencephalen Störungen. (Diagnostic significance of opto-kinetic nystagmus in commotio cerebri and other diencephalic disturbances.) A. M. Meerloo. 295.
*Une Forme Anatomo-Clinique Particulière de l'Alcoolisme Chronique : Cliniquement Rappelant la "Pseudo-Paralysie Générale" dese Anciens Auteurs, Anatomiquement Présantant une Sclérose Corticale Laminaire. (A clinico-anatomical form of chronic alcoholism, clinically resembling pseudo-general paralysis of ancient authors, anatomically presenting as laminal cortical sclerosis.) F. Morel. 305.
Positives Röntgenschattenbild eines extramedullären (psammösen) Meningeoms. (Positive X-ray picture of an extramedullary meningioma.) M. Ormos. 309.
Critique et Interprétation Rationelle du Principe de l'Intégration. (Critical and rational interpretation of the principle of integration.) W. Riese. 313.
Klinischer Beitrag zur Kenntnis der amyotropischen Lateralskelose. (Clinical contribution to the knowledge of amyotrophic lateral sclerosis.) L. Rubinstein. 320.
Einiges über das Gehirn der Hochtalente. (On the brain of the highly-talented.) K. Schaffer. 347.
Schizophrenie und Militärdienst. (Schizophrenia and military service.) J. Kläsi, H. W. Maier, B. Manzoni, H. Steck, and Stähelin. 353.

Psychodynamics of Compulsion Neurosis.—A case is described showing symptoms both of compulsion neurosis and manic-depressive psychosis. The author stresses the presence of compulsive thought in both conditions and the fact that in the first these are stripped of their appropriate affect. Cure of either condition may occur with persistence of the other. (H. de P.)

Bridge of Nose-Eyelid Reflex.—Investigations have been carried out on the diagnostic value and anatomico-biological foundations of reflexes. The reflex here discussed is obtained by striking the bridge or tip of the nose, and consists in simultaneous contraction of both orbiculares oculi. The author's material consisted of normal human beings and also those with lesions of the facial nerve and certain organic diseases of the C.N.S. He considers that his findings can be used for locating lesions of the facial nerve. (H. de P.)

Tumours of Third Ventricle.—Clinical manifestations are usually slight and often deceptive, and localizing signs more rare than in other cerebral tumours. Neurological examination often gives negative results. The tumour can only be recognized with certainty by ventriculography and this should be done in all suspected cases. (H. de P.)

Poisoning with Chlorine-Carbon Compounds.—The poisonous qualities of chlorine-carbon compounds are discussed with special reference to the protection of industrial workers engaged in the manufacture of these substances—notably trichlorethylene and tetrachloreltane. A case of chronic poisoning with trichlorethylene is described. He proceeded to investigate the incidence of such poisoning in different groups and advised against the employment of young people, women, and men over 45 with any tendency to arteriosclerosis, in such manufacture. Alcohol also produces hypersensitivity to substances of this group. (H. de P.)

Chronic Alcoholism resembling "Pseudo-General Paralysis."—Four cases showing an atypical form of chronic alcoholism are described, which resemble the "pseudo-G.P.I." of the ancient authors in both positive and negative features. These cases all had negative Wassermann reactions and signs of alcoholic gastritis; all had had attacks of atypical delirium tremens. Histological changes in the brain tissue are described which suggest the name "alcoholic laminary sclerosis." (H. de P.)

BOOK REVIEWS

SYMPOSIUM ON THE SYNAPSE

H. S. Gasser, J. Erlanger, D. W. Bronk, R. L. de Nó, and A. Forbes.

(Chas. C. Thomas, Springfield, Ill. 1939. Pp. 113. $2.00)

During the past few years there has been considerable controversy over the mechanism of synaptic transmission. One school believes that transmission depends upon the liberation of acetyl choline; the other holds that it is brought about by local electric circuits of the same type as those which propagate nervous impulses along axons. The "Symposium on the Synapse" was written with this controversy in mind. Dr. Gasser, Professor Erlanger, and Dr. Lorente de Nó appear to favour the electrical theory, for they stress the similarities between synapses and peripheral nerves; Dr. Forbes reviews the evidence for both theories, but commits himself to neither; while Dr. Bronk adopts a pluralistic view, in which acetyl choline, inorganic ions, and electric currents all contribute towards transmission across the synapse. The material considered covers a wide range and is not strictly confined to synaptic problems. After-potentials and recovery in peripheral nerve, the blockage of conduction, and the spatial distribution of bioelectric currents are among the subjects discussed. Much of the experimental work has already been described in scientific journals, but the articles by Dr. Lorente de Nó and Dr. Bronk are largely based on new material. Dr. Bronk is particularly interesting and gives an excellent account of the way in which electrolytes affect transmission through synapses in the sympathetic system. He also describes interesting experiments on summation, fatigue, and recovery in the stellate ganglion.

EPIDEMIC ENCEPHALITIS

Third Report by the Matheson Commission.

(Columbia University Press, New York. 1939. Pp. 493. $3.00)

The preparation of periodic surveys of the field of epidemic encephalitis has been one of the objects of the Matheson Commission. This Third Report brings the review of the literature up to the first half of 1938. There are included adequate reviews of the epidemiology of the St. Louis Type and Japanese B Encephalitis, and in these lies much of the merit of the volume. It is unfortunate that the bibliography should occupy more than half the book when the laboratory and clinical work of the Commission, which consisted in part in a follow-up study of encephalitic patients for long periods, should be scantily documented in a few pages. Some attempts at treatment have been based on Levaditi's suggestion that epidemic encephalitis may be due to a neurotropic form of a herpes virus. Results are presented for treatment with a formalinized herpes virus in the acute stage. " The case fatality of treated cases has been less than half that of the untreated cases. Moreover, the neurological conditions have seemed to disappear more rapidly in treated cases." Further data as to the effect of treatment on development of the chronic stage of the disease will make a contribution of importance in the study of the disease.

ELECTRICAL EXCITATION OF NERVE

B. Katz

(Oxford University Press, London. 1939. Pp. 151. 10*s.* 6*d.*)

This book is a review of recent advances in the study of excitable tissues. It begins with an account of the mathematical theories which have been used to describe the excitation process. Classical experiments showed that an electric current would not excite a nerve, unless it satisfied certain conditions. First, the stimulus must exceed a certain limiting strength ; secondly, it must rise at a minimal rate ; and, thirdly, a definite quantity of electricity must flow through the tissue. These facts are not easy to incorporate in a simple hypothesis, but the regularity of the excitation process encouraged many physiologists to propose comprehensive mathematical theories. The most well known are those of Hill, Monnier, and Rashevsky. Dr. Katz deals fully with these and emphasizes their basic similarity. He shows that they are capable of co-ordinating a large number of experimental facts, but break down when a detailed analysis is made. The second part of the book deals with the more recent physical concepts, which have to a certain extent replaced these theories. The cable-like structure of nerve is discussed and its importance emphasized. This leads on to the subject of conduction, and Dr. Katz shows how the information obtained in excitation studies can be used to explain the transmission of nervous messages. The final chapters contain a clear account of recent work on subthreshold action potentials and the initiation of nervous impulses. Dr. Katz's review will be of considerable interest to biophysicists, since it contains a great deal of information which has never been collected before. A possible criticism is that too much space is devoted to a consideration of empirical theories, which are known to be at variance with more recent observations. A second criticism, which applies more to the subject than to the book itself, is the complexity of the terminology. Only a specialist will avoid being confused by an array like the following : physiological electrotonus, heterochronism, hauptnutzzeit, subordination, etc. The author obviously feels this difficulty, but it would have been impossible to simplify the book without making it less comprehensive. Dr. Katz might have done this if his original manuscript had been written as a monograph ; but, as he explains in the preface, the review was first written at the invitation of the Ergebnisse der Physiologie, whose publishers finally refused it because the author was not of Aryan race.

SELECTED WRITINGS OF SIR CHARLES SHERRINGTON

Compiled and edited by D. Denny-Brown

(Hamish Hamilton Medical Books. 1939. Pp. 532. 25*s*.)

This work is a valuable and important contribution to neurological literature. It contains a very full selection of Sherrington's work and reprints, and the most important parts of many papers, some of which are not readily available.

Though all from the pen of Sherrington and his collaborators it gives a picture of the development of the physiology of the nervous system during the past sixty years and of the change in attitude to the nervous system that has occurred during his lifetime and owes so much to his own work. For this change is clear in this selection. First, concentration on anatomical relationships and the distribution of nerves and nerve roots. Then, as these were clarified, moving to concentration on their functional relationships and analysis of the control of movement and reflex activity leading to the concepts of central excitatory and inhibitory states. Finally, analysis of the relationship of excitation and inhibition at the synapse and of the activity of single neurones.

The selection has been well carried out to give a continuous and readable treatise rather than a number of juxtaposed cuttings. It has been edited by one of his distinguished pupils, who in his selection has brought out Sherrington's attitude to the nervous system, and his powers of making fundamental discoveries from simple but meticulously accurate observation. In reading some of the papers written forty years ago it is striking how they remain as valuable as when written owing to the extreme accuracy in description and practical detail. The editorial notes give briefly the necessary explanation of the context of parts of papers selected. The arrangement is in general chronological, with such departures as are necessary for continuity of subject-matter.

The earlier sections give Sherrington's work on nerve roots, their distribution and overlap, followed by mapping of reflex fields by stimulation of sensory nerves and roots. The next sections deal with the reflex reactions to induction shocks, and charting the fractional contraction of various muscles taking part in flexor reflexes. Next are given extracts from papers on inhibition and co-ordination followed by a full selection of work on postural reflexes, tonus, and the stretch reflex. This is perhaps the most satisfying of all reflex work in that Sherrington and Liddel were able to explore the central processes using a normal sensory stimulus, stretch of proprioceptive end organs. They thus avoided the artificialities of electrical excitation and yet were able to control and grade the stimulus with great precision. The reflexes involved were of much greater complexity than the flexion reflex to noxious stimulation, and a far more precise analysis was possible than in the case of the scratch reflex. Section IX contains extracts from papers on the cortex, localization, and facilitation. In Section X are full extracts from Sherrington's work with Eccles on the detailed analysis of the flexor reflex and observations of the behaviour of single motor units, which correlates Sherrington's work with that of Adrian on the detailed analysis of single nervous pathways. There are a number of line illustrations, and a full bibliography is appended. The passage selected as epilogue from the Rede Lecture is a happy expression of Sherrington's breadth of view and penetration to the realms of philosophy.

This book is a valuable work for students and neurologists and a worthy tribute to one who it is safe to say has done more to clarify the working of the nervous system than any other man.

NEUROLOGY

S. A. Kinnier Wilson

(Edward Arnold and Co., London. 1940. Pp. 1,838. £4 4*s*.)

In recent years there have been published throughout the world many text-books of neurology. In view of this spate, the neurologists of this country have often remarked on the absence of a modern authoritative work by a British author and the need for such a work expressive of the outlook of British neurology. This need has now been remedied by the publication of a work on neurology consisting of two volumes by the late Dr. Kinnier Wilson.

Known by his friends to have been busy in the compilation of such a work for many years, it was with deep regret that the news of his premature and unexpected death was received. Fortunately Dr. Wilson had collected much material and had already prepared before his death the text for a book on neurology. By carefully and scrupulously following his plans it has been possible for Dr. Ninian Bruce to complete this book for publication " to all extents unaltered and as it left Dr. Wilson's pen."

The reviewer is immediately impressed with the magnitude of the work, for in these two volumes is gathered together information of an encyclopædic character. The description of clinical entities are clear and succinct ; in them, too, is expressed Dr. Wilson's own view-point. Care has been taken to make the pathological information full yet concise, and the surveys of the experimental pathology will be invaluable —an addition which adds considerably to the value of the book. Therapeutic considerations have received close attention, and practitioners, as well as neurologists, seeking aid in this sphere of neurology will be well rewarded.

In Part I toxic infective diseases of the nervous system are dealt with. Herein are described meningitis, encephalitis, demyelinating conditions and myelitis, radiculitis and neuritis. The chapter given to disseminated sclerosis is very full and the various theories as to possible causation are fully discussed. It is to be regretted that an indication of the author's own view-point as to the possible cause is not readily available—this would have been welcomed. Also a note on comparative pathology might have enhanced this chapter. Part II deals with special forms of toxic infection of the nervous system which include neurosyphilis, tubercle, tetanus, herpes, rabies, and louping-ill. The chapters on neurosyphilis are most informative and clear ; therapy is adequately discussed and in detail. In Part III special forms of toxicosis of the nervous system are considered, such as alcoholism, morphinism, etc. The modern conception of alcoholic neuritis being the result of a deficiency receives adequate and critical analysis. Part IV, in the larger of the two volumes, contains descriptions of the varieties of familial and non-familial degenerative conditions. These chapters are of particular value, as these conditions were of great interest to the author and a field in which he carried out much original work ; for instance, his own work on progressive lenticular degeneration. The very wide grasp of the literature and personal experience of Dr. Wilson show clearly in these chapters. Part V—diseases of vascular origin—and Part VI—tumours of the nervous system—contain all matter that is relevant to these subjects. In Parts VII and VIII metabolic and congenital conditions are described. Epilepsy and migraine are treated at length and in detail in the following parts. The author's powers of description are shown to their best in these chapters, which merit reading by all members of the medical profession. The chapter given to family periodic paralysis is disappointing in that the more recent work on the chemical changes in the blood found in this condition and the treatment are not mentioned. It is to be remembered that with a work of this magnitude, material may have been in the hands of the printers before the publication of the investigations on the biochemical disturbances found in this rare disease and that this is a criticism to which any book may be open. The neuroses are

dealt with in the last part. It is unfortunate that the author has not seen it possible to devote more space to his views on these conditions. An excellent index and abundant references to the literature augment the usefulness of the book.

This is a book which should find a place in the library of every neurologist throughout the world, for in it information is collected in a manner to be found nowhere else. As a book of reference it will prove inestimable ; as an aid to specialist and teacher it stands unique.

RECENT ADVANCES IN NEUROLOGY

W. Russell Brain

(J. and A. Churchill, Ltd., London. 1940. Pp. 364. 15*s*.)

Another addition of this very useful book appears. Several additional chapters have been included. The new chapters on headache and electro-encephalography are of particular interest. In the chapter on neurotropic viruses the treatment of anterior poliomyelitis with serum is critically discussed. The reader, however, does not receive real guidance as to the value of this form of therapy, as the author is careful not to express any precise views. A guide to general practitioner and neurologist on this point would have been invaluable. The reproductions of X-ray films are disappointing and this should be corrected in future additions. A more complete index would make reference more easy.

THE LANGUAGE OF GESTURE

Macdonald Critchley

(Edward Arnold and Co., London. 1939. Pp. 128. 5*s*.)

The language of gesture is of such common and constant usage that its importance must often pass unnoticed. Yet speech itself without its accompanying gesture of expression is an unlovely monotone. In the theatre mime and gesture are of supreme value ; the difference in their quality is the difference between an expert and an unskilled performance. The author's interest in the subject was attracted by the case of a deaf mute who had sustained a small vascular lesion in the left hemisphere which, although there was no paralysis, resulted in a defect in the powers of expression by way of his accustomed sign talk. He discusses the relationship of gesture and speech, and concludes that the two faculties seem to have developed side by side rather than that one is a forerunner of the other. There is an excellent chapter on the neurology of gesture in which variations of a pantomime and gesture in abnormal neurological and psychiatric states are discussed. The subject is reviewed from many other aspects, including a comparison of the sign language of different races. Dr. Critchley has written an interesting and stimulating book which will well repay the attention of both doctors and laymen.